






## Review

# Show Me What You Have Inside—The Complex Interplay between SIBO and Multiple Medical Conditions—A Systematic Review

Natalia Sroka <sup>1,\*</sup> , Alicja Rydzewska-Rosołowska <sup>1</sup> , Katarzyna Kakareko <sup>1</sup> , Mariusz Rosołowski <sup>2</sup> , Irena Głowińska <sup>1</sup> and Tomasz Hryszko <sup>1</sup> 

<sup>1</sup> 2nd Department of Nephrology and Hypertension with Dialysis Unit, Medical University of Białystok, 15-276 Białystok, Poland

<sup>2</sup> Department of Internal Medicine and Hypertension, Medical University of Białystok, 15-540 Białystok, Poland

\* Correspondence: natalia.sroka321@gmail.com

**Abstract:** The microbiota, as a complex of microorganisms in a particular ecosystem, is part of the wider term—microbiome, which is defined as the set of all genetic content in the microbial community. Imbalanced gut microbiota has a great impact on the homeostasis of the organism. Dysbiosis, as a disturbance in bacterial balance, might trigger or exacerbate the course of different pathologies. Small intestinal bacterial overgrowth (SIBO) is a disorder characterized by differences in quantity, quality, and location of the small intestine microbiota. SIBO underlies symptoms associated with functional gastrointestinal disorders (FGD) as well as may alter the presentation of chronic diseases such as heart failure, diabetes, etc. In recent years there has been growing interest in the influence of SIBO and its impact on the whole human body as well as individual systems. Therefore, we aimed to investigate the co-existence of SIBO with different medical conditions. The PubMed database was searched up to July 2022 and we found 580 original studies; inclusion and exclusion criteria let us identify 112 eligible articles, which are quoted in this paper. The present SIBO diagnostic methods could be divided into two groups—invasive, the gold standard—small intestine aspirate culture, and non-invasive, breath tests (BT). Over the years scientists have explored SIBO and its associations with other diseases. Its role has been confirmed not only in gastroenterology but also in cardiology, endocrinology, neurology, rheumatology, and nephrology. Antibiotic therapy could reduce SIBO occurrence resulting not only in the relief of FGD symptoms but also manifestations of comorbid diseases. Although more research is needed, the link between SIBO and other diseases is an important pathway for scientists to follow.

**Keywords:** SIBO; gut microbiota; dysbiosis; LPS; breath test; rifaximin



**Citation:** Sroka, N.; Rydzewska-Rosołowska, A.; Kakareko, K.; Rosołowski, M.; Głowińska, I.; Hryszko, T. Show Me What You Have Inside—The Complex Interplay between SIBO and Multiple Medical Conditions—A Systematic Review. *Nutrients* **2023**, *15*, 90. <https://doi.org/10.3390/nu15010090>

Academic Editors: Peng Chen, Xingyin Liu and Wenke Feng

Received: 19 November 2022

Revised: 18 December 2022

Accepted: 20 December 2022

Published: 24 December 2022



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

The term microbiome is generally used to define the set of all genetic material of a microbial community. On the other hand, the microbiota is commonly described as a complex of microorganisms in a particular environment. The human gut microbiota inholds above 1500 species spread in more than 50 phylas [1], but it is dominated mainly by two of them—Bacteroidetes and Firmicutes [2]. The intestinal bacteria have a multidirectional impact on individual organs and the whole body by the synthesis of diverse metabolic products or supporting prevention from the invasion of pathogens by colonizing mucosal surface [3]. Bacterial equilibrium is crucial in the maintenance of immunity and homeostasis of the organism. Dysbiosis, as a disturbance in bacterial balance, might trigger or exacerbate the course of different pathologies.

Small intestinal bacterial overgrowth (SIBO) is a condition defined by the number of colonic-type bacteria in the small gut equal or greater than  $10^5$  colony forming units

per milliliter (CFU/mL) as well as an alteration in the standard ratio of small bowel microbiota [4]. Common complaints in patients with SIBO are general manifestations and gastrointestinal (GI) symptoms like abdominal pain or defecation rhythm disturbances. Higher permeability for lipopolysaccharide (LPS) is mentioned as the main cause of underlying pathology, which leads to stimulation of inflammatory response and chronic proinflammatory status. Conditions concomitant with SIBO may predispose to the development of intestinal dysbiosis itself. Disorders in the structure and functionality of the intestinal wall as a result of disease or its treatment, higher than normal concentrations of substances like ghrelin, leptin, TMAO (trimethylamine-N-oxide), or the presence of pro-inflammatory cytokines could take part in the induction and development of SIBO.

The jejunal aspirate is known as the gold standard for diagnosing SIBO. However, breath tests (BTs) with glucose or lactulose (glucose breath test [GBT] or lactulose breath test [LBT] respectively) are used more often, because of their non-invasiveness [5].

In recent years there has been growing interest in the influence of gut microbiota, especially SIBO, and its impact on the whole human body as well as individual systems. The objective of our research was thus to investigate and systematize the relationships mentioned above. To better understand these relations, we performed a review of the literature.

## 2. Materials and Methods

For the identification of relevant publications, a standardized search strategy was used. The PubMed database was searched up to July 2022 with the terms “SIBO”, “Small Intestinal Bacterial Overgrowth”, “gut microbiota”, “gut bacteria”, “microbiome”, “microbiota”, “dysbiosis”, “breath test”, “gut axis” in various combinations with the terms “related”, “altered”, “treatment”, and “disease”. Based on these results we could determine which body systems to focus on. Subsequently, we broadened our trawl by linking the term “SIBO” with specific organs or diseases: “H.pylori infection”, “IBS”, “IBD”, “Crohn’s disease”, “Colitis ulcerosa”, “celiac disease”, “obesity”, “abdominal surgery”, “NAFLD”, “cirrhosis”, “gallstone”, “pancreas”, “pancreatitis”, “cystic fibrosis”, “heart failure”, “atherosclerosis”, “coronary artery disease”, “DVT”, “diabetes”, “thyroid”, “hypothyroidism”, “hyperthyroidism”, “Parkinson”, “brain fogginess”, “systemic sclerosis”, “rosacea”, “kidney”, “CKD”, “AKI” and “IgA nephropathy”. Additional publications were retrieved from citations of manuscripts found in the above search.

## 3. Results

The search strategy lets us identify 580 articles. Publications were included if they assessed SIBO in humans. Studies were limited to original articles available in the English language. Dual papers and titles not relevant to the research question were excluded. Review articles, metaanalyses, meeting abstracts, case reports, editorials, and commentaries were excluded as well. We also excluded articles, when the main test group had taken: (a) antibiotics, (b) probiotics, (c) IPP. Finally, we identified 112 eligible articles, which are included in this paper. A schematic PRISMA flow diagram for the selection of the studies included in this review is presented in Figure 1. Additionally, quoted articles were categorized and summarized in Table 1.

**Table 1.** Original studies investigating the co-existence of SIBO with different disorders.

Disorder	Years of Publications		Number of Studies	Authors, References
Gastroenterology				
Helicobacter pylori infection		2017	1	Enko et al. [6]
Irritable bowel syndrome		1991–2016	14	Pimental et al. [7], Pimental et al. [8], Walters et al. [9], Lupascu et al. [10], Posserud et al. [11], Bratten et al. [12], Park et al. [13], Parodi et al. [14], Ghoshal et al. [15], Rana et al. [16], Sachdeva et al. [17], Ghoshal et al. [18], Abbasi et al. [19], Zhao et al. [20]
Inflammatory bowel disease	Crohn’s disease	1981–2018	5	Rutgeerts et al. [21], Castiglione et al. [22], Klaus et al. [23], Greco et al. [24], Ricci et al. [25]
	Ulcerative colitis	2014, 2021	2	Rana et al. [26], Yang et al. [27]
	Both	2013–2016, 2022	4	Rana et al. [28], Lee et al. [29], Andrei et al. [30], Ghoshal et al. [31]
Celiac disease		1970; 2002–2015	7	Prizont et al. [32], Tursi et al. [33], Ghoshal et al. [34], Rana et al. [35], Rubio-Tapia et al. [36], Chang et al. [37], Lasa et al. [38]
Abdominal surgery		2011–2020	6	Paik et al. [39], Heneghan et al. [40], Sabate et al. [41], Kim et al. [42], Rao et al. [43], Mouillot et al. [44]
Obesity		2008–2018	4	Sabate et al. [45], Madrid et al. [46], Fialho et al. [47], Roland et al. [48]
Non-alcoholic fatty liver disease		2001–2017	8	Wigg et al. [49], Sajjad et al. [50], Miele et al. [51], Shanab et al. [52], Fialho et al. [53], Ghoshal et al. [54], Mikolasevic et al. [55], Shi et al. [56]
Cirrhosis		1991–2016	11	Chesta et al. [57], Casafont Morencos et al. [58], Madrid et al. [59], Yang et al. [60], Bauer et al. [61], Gunnarsdottir et al. [62], Nancey et al. [63], Pande et al. [64], Jun et al. [65], Gupta et al. [66], Zhang et al. [67]
Gall stone disease		2014, 2018	2	Kaur et al. [68], Kim et al. [69]
Chronic pancreatitis		1985–2019	8	Casellas et al. [70], Trespi et al. [71], Signoretti et al. [72], Kumar et al. [73], Kim et al. [74], Ni Chonchubhair et al. [75], Lee et al. [76]
Acute pancreatitis		2017, 2020	2	Zhang et al. [77], Kim et al. [78]
Cystic fibrosis		2009–2019	3	Lisowska et al. [79], Dorsey et al. [80], Furnari et al. [81]
Cardiology				
Heart failure		2016, 2021	2	Pasini et al. [82], Song et al. [83]
Atherosclerosis		2017, 2018	2	Ponziani et al. [84], Fialho et al. [85]
Deep vein thrombosis		2016, 2017	2	Fialho et al. [86], Cheng et al. [87]
Endocrinology				
Diabetes	Type 1	2009, 2013, 2018	3	Ojetti et al. [88], Faria et al. [89], Malik et al. [90]
	Type 2	2011, 2017	2	Rana et al. [91], Rana et al. [92]
	Both	2000, 2002	1	Zietz et al. [93]
Thyroid disorders		2007, 2017, 2018	3	Lauritano et al. [94], Brechmann et al. [95], Konrad et al. [96]
Neurology				
Parkinson disease		1996–2020	7	Gabrielli et al. [97], Dobbs et al. [98], Fasano et al. [99], Tan et al. [100], Niu et al. [101], Su et al. [102], Hasuike et al. [103]
Autism		2018	1	Wang et al. [104]
Brain fogginess		2018	1	Rao et al. [105]
Rheumatology and cutaneous disaeses				
Systemic sclerosis		1980–2020	9	Parodi et al. [106], Marie et al. [107], Fynne et al. [108], Savarino et al. [109], Gemignani et al. [110], Marie et al. [111], Adarsh et al. [112], Sawadpanich et al. [113], Garcia-Collinot et al. [114]
Rosacea		2008, 2016	2	Parodi et al. [115], Drago et al. [116]
Nephrology				
Chronic kidney disease		2003	1	Strid et al. [117]

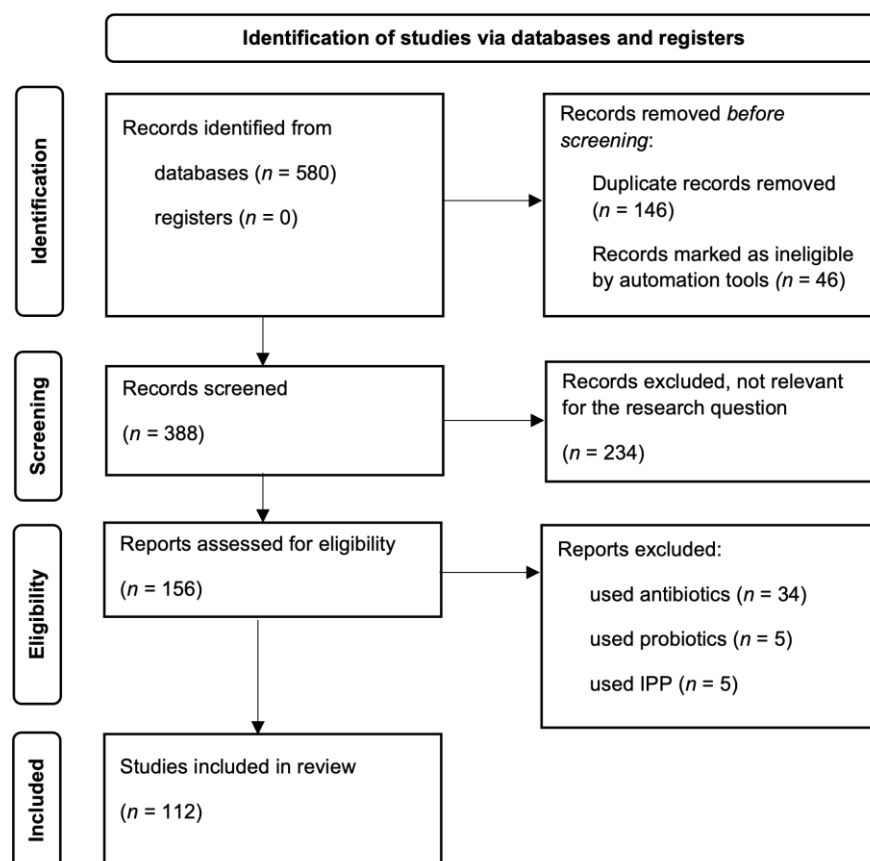


Figure 1. Search strategy and results.

## 4. Discussion

### 4.1. Definition and Pathophysiology

Small intestinal bacterial overgrowth is a disorder characterized by differences in quantity, quality, and location of the small intestine microbiota [5]. The excess bacterial population in the small bowel (the standard definition is  $10^5$  CFU/mL of proximal jejunal aspiration) is accompanied by the appearance of Gram-positive and Gram-negative aerobic organisms as well as anaerobes, which are usually more common in the colon [118,119]. The main bacteria associated with SIBO include *Streptococcus*, *Staphylococcus*, *Bacteroides*, *Lactobacillus*, and *Enterobacteriaceae*—*Escherichia*, *Klebsiella*, or *Proteus* [120].

Patients suffering from SIBO usually complain of general symptoms like weight loss, weakness, and other manifestations specific to the gastrointestinal tract—abdominal pain, bloating, diarrhea, constipation, and belching. Disturbances in the gut lumen are induced by bacterial overgrowth, which entails nutritional deficiencies. Increasing malabsorption exacerbates the condition and leads to more severe complications like anemia, fat-soluble vitamin deficiencies, or hypoproteinemia [5]. Thereupon SIBO could be diagnosed in symptomatic patients when proximal jejunal aspirate contains  $>10^3$  CFU/mL [121].

The digestive system possesses different mechanisms preventing the excess of small intestine microbiota. Many factors influence the development of SIBO: gastrointestinal motility, gastric acid and pancreatobiliary secretion, anatomy of the tract, and the immunological system. The most important of these—motility, includes stomach emptying as well as peristaltic movements in the small bowel which may result in the delayed transition of bacteria to the colon. Gastric acid, as the first guarding mechanism, limits the quantity of bacteria in the gut, by creating a hostile environment for bacterial population growth [5,119]. The other protector is the ileocecal valve—its lower pressure is highly associated with SIBO occurrence [122].

#### 4.2. Diagnosis

Initially, SIBO used to be diagnosed together with other abnormalities of the GI tract, including postsurgical changes. Nowadays, mostly due to its non-specificity and often asymptomatic course, a symptom-based diagnosis encounters some difficulties. Thus, it was crucial to find a proper diagnostic technique. The present methods could be divided into two groups—invasive, including the gold standard—small intestine aspirate culture and non-invasive, breath tests [4].

The number of aerobic and anaerobic bacteria per milliliter of jejunal aspirate equal to or greater than  $10^5$  suggests SIBO [123]. According to The North American Consensus on Breath Testing it is advised to apply lactulose or glucose pending BT; an increase of either hydrogen level 20 p.p.m. from baseline by 90 min or methane level 10 p.p.m on BT for both carbohydrates is considered positive [121].

Although endoscopy, due to its directness, is acknowledged as the gold standard for diagnosing SIBO, it carries several disadvantages [4]. Besides performing the actual procedure, significant other problems emerge: high cost, the additional risk for the patient, improper sample collection leading to contamination by oropharyngeal flora, and lack of transparent cutoff determining a positive aspirate. On the other hand, breath tests are characterized by lower sensitivity (52–63% for GBT, 31–68% for LBT) and specificity (82–86% for GBT, 44–100% for LBT) [5]. Subjects are advised to prepare correctly for the examination which creates the greatest impediment. It is important to avoid antibiotics for four weeks before BT and promotility medications as well as laxatives one week before. Consuming complex carbohydrates is forbidden on a preceding day, fasting time should be about 8 to 12 h and smoking is not allowed on the day of BT. Pro- and prebiotics as well as proton pump inhibitors (PPI) are not limited, but the latter is not recommended on the test day [121]. Most reliable results are obtained when patients abide by all those rules.

Interestingly, not only BT or jejunal aspirate could be considered to investigate overgrowth in the small intestine. Increased fecal calprotectin concentration was found in subjects with systemic sclerosis and was connected with SIBO occurrence. Fecal calprotectin may be considered as a prospective, non-invasive test in SIBO diagnostics [111].

#### 4.3. Prevalence in Other Conditions

SIBO could be the only diagnosis in a patient, but it frequently accompanies or is accompanied by other conditions. The first connection was other disorders of the gastrointestinal system, subsequently, the relationship between SIBO and other systemic diseases was considered.

##### 4.3.1. Gastroenterology

The digestive system is highly exposed to many microorganisms; hence it evolved complex defense mechanisms. Dysfunction of protective barriers may lead to the development of SIBO. Hypochlorhydria, as a result of a decrease of gastric juice in the course of aging, abuse of PPI [124,125], or colonization with Gram-negative *Helicobacter pylori*, are well-known risk factors for excess of gut bacteria [119,126]. A rise in the gastric pH yields dysbiosis in the stomach and small bowel [127]. Moreover, Enko and Kriegshäuser observed that patients with *H. pylori* infection and positive  $^{13}\text{C}$ -urea breath test ( $^{13}\text{C}$ -UBT) have an even higher risk of SIBO [6].

The occurrence of many bowel diseases correlates significantly with the quantity and quality of small intestine flora. Manifestations similar to SIBO are observed in irritable bowel syndrome (IBS) multifactorial disease, therefore initially both were associated together. An activation of the immune system and expansion of inflammatory bodies in intestinal mucosa [128] and lamina propria [129] are observed in a course of IBS. These mechanisms may implicate the mucosal wall and increase intestinal permeability [10,13]. On the other hand, the presence of SIBO triggers immune activation as well [130]. Therefore, there are plenty of studies describing the co-occurrence of IBS and SIBO [7,8,11,12,15,17,19]. However, there is a big problem with the selection of a suitable method of diagnosis be-



tween breath tests and jejunal aspirate. LBT seems to create the most discrepancies [9,16,20] but combined with scintigraphic orocecal transit could achieve actual results [20]. Chronic diarrhea, constipation, abdominal pain, or bloating are present without a tangible cause. It was discovered that SIBO appeared less often in IBS-constipation subtype than in those with diarrhea [18]. In many patients, remission or reduction of symptoms after therapy with rifaximin was demonstrated, which may indicate SIBO as a causative factor of IBS [7,14,131]. The SIBO-IBS hypothesis is an interesting one and warrants more investigation.

Consequently, scientists took a closer look at inflammatory bowel diseases (IBD). The more frequent prevalence of SIBO with Crohn's disease (CD) than ulcerative colitis (UC) was observed in the majority of research [21,24,25,28–31]. Simple explanations could include easier access to the small bowel (mainly in CD), frequent fistulas and strictures, and sometimes required remedial surgical procedures even with resection of the ileocecal valve, which have a serious impact on intestinal motility [23]. On the other hand, the elevation of pro-inflammatory cytokines (IL-6, IL-8, TNF-alpha) and anti-inflammatory cytokine (IL-10) is observed in UC. Intestinal inflammation might damage enteric nerves or smooth muscles which leads to altered GI motility [26]. Both mechanisms are responsible for the prolongation of orocecal transit time (OCTT) and increased SIBO incidence in patients with IBD [22,26,28]. Interestingly, activity scores of Crohn's disease, as well as ulcerative colitis, could be diminished by rifaximin treatment which significantly improves patients' quality of life [132,133]. Additionally, Yang et al. affirmed better clinical efficacy of mesalazine after eradication of SIBO with rifaximin [27].

Celiac disease seems to certainly correlate with intestinal microbiota composition. The connection between SIBO and celiac disease has been studied since 1970 and the prevalence of SIBO was as high as 66.66% according to published data [32–35,38]. Precursory studies implied that due to GI dysmotility, the patient's condition was further complicated by the presence of gut dysbiosis. Cholecystokinin is a hormone responsible for stimulations of intestinal motility and its downregulation in the celiac population is mentioned as one of the causes of dysmotility [134]. Moreover, some studies showed in these patients greater concentration of neurotensin—an inhibitor of upper GI peristalsis [135]. Additionally, intraepithelial lymphocytes are mediators of mucosal damage in SIBO and celiac disease, which implies a role of gut bacteria in the pathogenesis [136]. Eradication of SIBO with rifaximin yielded remission of symptoms in patients that had not responded to gluten-free diet [33]. Surprisingly, further studies showed no response to antibiotic therapy and a lower prevalence of SIBO in celiac disease, which was confirmed by aspirates of bacterial culture from small bowel—the gold standard of diagnosis [36,37]. Contrary to expectations, both conditions might exist independently.

Abdominal or pelvic surgery is also considered a risk factor for excess of gut bacteria [39,42,43]. Gastrectomy entails a decrease in gastric acid production [42], while cholecystectomy affects biliary secretion. Moreover, several ventral surgeries could induce disorders in GI structure and motility. Additionally, Kim et al. observed dependence between the type of the procedure and an increase in H<sub>2</sub> concentration during BT, which was the highest after gastrectomy [42]. Similarly to other conditions, oral rifaximin diminishes gastrointestinal complaints suggesting a role of gut dysbiosis in the pathogenesis of symptoms [40,43]. Nowadays, as bariatric procedures become the crucial treatment of obesity, and its use becomes widespread, data show disturbed intestinal motility in those patients [41,44]. Approximately 80% of individuals after bariatric surgeries suffer from symptomatic SIBO [44] and the highest proportion is found after Roux-en-Y gastric bypass [41]. It might be associated with greater weight loss than in other bariatric procedures [41].

However, obesity in a multifactorial way can also be a cause of SIBO. First of all, abnormal levels of leptin and ghrelin were observed in obese people, which fosters dysmotility [46]. Secondly, cluster contractions of myenteron as a result of the increase of intestinal Migrate Motor Complex (MMC), typical for small bowel obstruction and common in advanced liver cirrhosis, were noticed as well [46–48]. On the other hand, the

difference in the composition of excess gut microbiota between obese and non-obese patients might influence the function of the intestinal mucosa (decline in the proportion of Bacteroides to Firmicutes). It leads to increased calorie intake, accumulation of fat in the adipocytes by greater production of short-chain fatty acids, and rise of ratio of visceral to subcutaneous fat area [47], as well as an increase of gut permeability for LPS and endotoxins, what leads to chronic proinflammatory status. This vicious circle is observed in SIBO and obesity as a constellation of different relationships. Additionally, a higher prevalence of intestinal dysbiosis in people suffering from metabolic syndrome was established during studies on SIBO and adiposity [47].

Solid organ dysfunction might also have an impact on the prevalence of dysbiosis in the small gut, mainly by affecting GI motility [62]. Non-alcoholic fatty liver disease (NAFLD), which could transform into non-alcoholic steatohepatitis (NASH), end-stage of liver dysfunction, or even hepatocarcinoma is the most widespread liver disorder in developed Western countries [137]. Obesity, as well as metabolic syndrome and type 2 diabetes mellitus, are the main risk factors for NAFLD [138]. Hence, similar implications of intestinal dysbiosis as mentioned above were noticed. A lower concentration of Bacteroides (which is lacking genes responsible for choline metabolism) was noticed in NASH patients irrespectively of BMI and fat intake [139]. Moreover, disorders of choline metabolism due to an increase of trimethylamine-N-oxide (TMAO) in the systemic circulation, lead to imbalanced lipid homeostasis [140]. Furthermore, several studies report a permanent elevation of the concentration of endogenous ethanol, which could be explained by increased fermentation in the gut lumen [141]. All those factors might be implicated in the development of NAFLD. A high prevalence of SIBO is observed in NAFLD population [49–56]. SIBO, by inducing an immunological fluctuation, could lead to chronic inflammation, mitochondrial disorders, a cumulation of lipids in hepatocytes, and NASH. However, most of the recent evidence is based on animal subjects or small human studies, so the relationship between gut microbiota and NAFLD is still more hypothesized than established.

SIBO is frequently diagnosed in liver cirrhosis [61–63,67] and it is associated with its severity [64,67], like the occurrence of hepatic encephalopathy or ascites and the Child-Turcotte-Pugh class. In various studies, the prevalence of SIBO is greater in patients with Child's C than Child's A cirrhosis [57–60,64]. Intestinal permeability and immunodeficiency predispose to a proinflammatory condition even without an obvious source of infection. Thereupon, the risk of development of spontaneous bacterial peritonitis is greater in the presence of SIBO in cirrhotic patients [65,66]. Moreover, ascites and increased serum bilirubin concentration could forecast the presence of SIBO [64].

Additionally, parenchymatous liver dysfunction is a risk factor for gallstone disease. Until present, only a few studies have been published, that compare it with SIBO. Both disorders are characterized by similar manifestations, like abdominal discomfort, nausea, belching, bloating, or fullness in the stomach after eating. Kim et al. observed a higher concentration of exhaled hydrogen and a prevalence of SIBO in subjects with gallstones [69]. The primary cause is speculated to be the result of dysfunction of gallbladder mucosa and the decreased secretion and antibacterial impact of bile in the GI tract due to excessive numbers of intestinal microbiota. On the other hand, one of the bile acids—deoxycholate—is produced from cholate in the gut lumen by gram-positive anaerobes. Prolonged OCTT entails a rise of deoxycholate absorption and imbalanced composition of bile, which becomes more lithogenic [68,69]. However recent studies have not yet explained the link between increased OCTT and serum bile acids.

Another organ potentially influenced by intestinal bacterial disorders is the pancreas. Chronic pancreatitis (CP) is a worldwide multifactorial disease with a high mortality [142]. Similar manifestations of CP and SIBO, like abdominal pain, diarrhea, or bloating suggest a connection between both. The studies revealed a higher prevalence of excessive numbers of bowel microbiota in CP patients than in healthy ones, regardless of etiology and it was associated with the Mayo Score [74,76]. Diabetes mellitus [75] and pancreatic exocrine insufficiency could also contribute to the progress of SIBO. Several mechanisms are proposed.

Firstly, decreased secretion of the pancreatic juice, which has antimicrobial functions as well, could promote the overgrowth of gut bacteria and malabsorption [73]. Furthermore, observed prolonged OCTT could be evoked by diabetes neuropathy, opioid intake, or maldigestion. Pancreatic enzyme replacement therapy (PERT) is crucial in CP treatment. Interestingly, the persistence of abdominal symptoms after PERT suggests SIBO as the etiology of exacerbation of the disease [73]. Frequently the condition is improved after empiric therapy with rifaximin [71,73]. However, all authors highlight the heterogeneity and the small number of test groups, which might have affected the results. Moreover, also a discrepancy between glucose and lactulose BTs exists. The latter shows a higher number of SIBO diagnoses in the CP group, probably caused by faster lactulose transit to the colon than expected and most results are considered as false positive [143], therefore glucose BT is preferable [70].

Studies also exist linking acute pancreatitis to gut microbiota. Although the duration of manifestations is not long, even 24 h is enough to initiate disturbances in the gut homeostasis [144]. The main reasons appear to be GI tract hypomotility with higher bowel permeability as well as decreased exocrine function and carbohydrates digestion due to acute pancreatitis (AP). A hospitable environment for the expansion of microbiota is created by these mechanisms [77,78]. The consequence is endotoxemia which yields a higher risk of complications like necrosis or secondary infection of the pancreas and mortality. The severity of AP correlates with the prevalence of SIBO [77].

Cystic fibrosis (CF) is a genetic disorder, which significantly affects the digestive system. Mutation of the CFTR gene leads to decreased secretion of fluid and bicarbonate from epithelium and accumulation of abnormal, concentrated mucus in the intestinal lumen. Thickened mucus is responsible for prolonged OCTT. Moreover, damage of Paneth cells, present in CF, affects small intestine motility as well [79,145]. Pancreas dysfunction and all factors mentioned above predispose to an excessive number of intestinal microbiota. The prevalence of SIBO in CF approaches 30% to 50% [145] and it might exacerbate gastrointestinal symptoms in CF. Because of similar manifestations, it is difficult to discern between both conditions. A huge bacterial burden may induce mucus secretion and impair its function. Empiric antibiotic treatment with rifaximin or metronidazole in CF results in improved digestion and absorption of nutrients as well as weight gain and appetite improvement [80,81]. Probiotic therapy may also amend the quality of life in the CF population by positive impact not only on GI but also on respiratory function by reducing pulmonary inflammation [80,81,146]. Unfortunately, the majority of studies were performed on animals and further research is crucial to understand and establish the dependence between SIBO and CF.

#### 4.3.2. Cardiology

The gastrointestinal tract may seem, at first glance, to be the only target of SIBO signs and symptoms but scientists have explored its connections with other organs and systems. One of them was the cardiovascular system. Heart failure (HF) has considerable effects on the gut bacteria [147]. Co-existence of both entities, disturbances of the gut microbiota equilibrium as well as prevalence and severity of HF were examined in a lot of studies [82,148]. Ischemia of the small intestine wall can be caused by a decreased output of the heart [148,149]. Consequently, it may lead to bowel dysfunction, and higher intestinal permeability, and correlate with the severity, complications, and progression of HF [82,147,149,150]. The possible trigger might be lipopolysaccharide (LPS)—one of the components of Gram-negative bacteria, classified as a proinflammatory factor,—its high concentrations, were confirmed in HF patients with oedema [151]. A well-known endotoxin, it connects with toll-like receptor 4 (TLR-4) and activates an inflammatory cascade due to myocardial disorders such as dysfunction and remodeling of left ventricular and intensified cardiac muscle cells apoptosis [152,153]. GutHeart, a randomized clinical trial, investigates if external interference in intestinal microbiota can improve heart function. Patients are divided into three groups, treated with a placebo, probiotic (*Saccharomyces*



boulardii), or antibiotic (rifaximin). Although the final results of GutHeart are still pending, the first analysis seems to confirm its thesis and indicate a new trend in HF treatment [154]. Recently, Song et al. confirmed a high prevalence of SIBO in HF population, as well as SIBO, was related to worse implications [83].

Trimethylamine-N-oxide (TMAO) is as a pro-atherosclerotic metabolite of phosphatidylcholine [155]. The production of TMAO is dependent on the metabolic pathway of intestinal bacteria, which are responsible for the transformation of phosphatidylcholine into trimethylamine and the latter is oxidized by hepatic enzymes to TMAO [155,156], which has a great impact on atherosclerosis development and increases the risk of chronic vascular disease [140]. No studies prove a direct correlation between TMAO levels and SIBO occurrence, however, Fialho et al. observed TMAO elevation in SIBO-positive patients with NAFLD [53]. Moreover, the results of breath tests of subjects with coronary artery disease (CAD), show a correlation between the prevalence of SIBO and CAD as well as the number of arteries affected by the disease [85]. Interestingly, the elevation of inactive matrix Gla-protein and arterial stiffening was reported in patients with SIBO [84]. Similarly to heart failure, proinflammatory agents are responsible for the induction, development, and exacerbation of CAD [53,84].

Deep vein thrombosis (DVT) may also be associated with SIBO, especially due to the increased concentration of inflammatory factors and expression of TLR-4 by platelets and endothelial cells. Pro-coagulatory activity is induced by combining TLR-4 with LPS; accordingly, SIBO is named as an individual risk factor for DVT [86]. On the other hand, the abundance of cytokines and interleukins in DVT may stimulate the intestinal immune system and alter microbiota in the gut lumen, which indicates DVT as a risk factor for SIBO. A bidirectional relationship between both conditions is highlighted in quoted studies [86,87]. Additionally, the authors advise careful observation of patients with intestinal dysbiosis for findings resembling DVT [86].

#### 4.3.3. Endocrinology

Patients suffering from diabetes mellitus (DM), frequently present with gastrointestinal manifestations like diarrhea, constipation, or flatulence [89,157]. The type of DM is defined by its etiology. Type 1 develops due to the destruction of  $\beta$ -cells in the pancreas, type 2 as a consequence of insulin resistance. After birth gut microbiota plays an important part in the development of the immune system. Firstly, intestinal dysbiosis leads to a dysfunctional immunological response, inducing damage to  $\beta$ -cells. Moreover, higher permeability is also provoked by disturbed bacterial homeostasis in the bowel and the availability of different bacterial antigens which promotes the immune system to destroy  $\beta$ -cells as well. Similarly, in type 2 DM endotoxemia, following the presence of LPS in the bloodstream, induces the production and causes a release of cytokines, which may destroy insulin receptors in the targeted tissue and provoke the onset of type 2 DM [158,159]. These hypotheses could partly explain the role of abnormal microbiota in DM pathogenesis. On the other hand, diabetes itself might influence the intestinal microbiome. It is associated with autonomic neuropathy and acute hyperglycemia, which may provoke disturbances of GI motility, which include delay of gastric emptying and OCTT [89–93,160]. Gastroparesis, as a complication of DM, develops due to the dysfunction of Phase 3 MMC and is often accompanied by SIBO, notably with protracted persistence of symptoms [161]. The prevalence of SIBO in both types of diabetic patients was significantly higher than in the general population. Autonomic neuropathy increases the prevalence of SIBO as well as insulin requirements [88]. In addition, the persistence of dysbiosis could exacerbate diabetes. Interestingly, early results show positive effects of treatment with prebiotics, probiotics, and antibiotics as well as a decrease of GI symptoms in patients with diabetes [162,163].

Merely a few studies about the relationship between the thyroid gland and altered gut microbiome have been published but interesting concepts are being investigated. Endocrine disorders are often accompanied by GI symptoms like abdominal discomfort, constipation, or diarrhea. Hypothyroidism could be a causative factor of hypomotility [164] and due to

that SIBO is detected in over 50% of patients with thyroid insufficiency [165]. However, reasons are still vague and different hypotheses like bowel oedema [166] or decreased number of  $\beta$ -adrenergic receptors and myoelectrical function are suggested [94] but also these need more investigations. In one study, massive overgrowth of small intestinal bacteria was considered to influence the neuromuscular system, but the concentration of thyroid hormones was not dependent on the gut microbiota [94]. Surprisingly, Brechmann et al. implied that supplementation of levothyroxine highly interferes with SIBO, even more than hypothyroidism [95]. Hyperthyroidism could influence GI motility as well. Studies propose ghrelin as a causative factor for this, but explanations are still unclear. Differences in the composition of intestinal microbiome between patients suffering from hyperthyroidism and healthy controls have been found, however, results have not established a definite correlation [167]. There are also some suggestions that immune and autoimmune systems could be induced by bacterial antigens and provoke the onset of Graves and Hashimoto disease in genetically susceptible individuals. Dysbiosis modifies the immunological response, which promotes inflammation and leads to vulnerability of the gut wall, increase of intestinal permeability, and endangering of antigens [168]. Both conditions are characterized by the presence of antibodies, which in the first case promote hyperactivity of the thyroid, in the other one the chronic inflammation and destruction of the gland leading to hypothyroidism. Nowadays, good dietary habits play an important role in the improvement of intestinal microbiota, which could lead to a reduction of inflammation. Consumption of optimal amounts of polyunsaturated and omega-3 fatty acids, fiber, or foods rich in secondary plant metabolites (cocoa, honey, fruits, and vegetables) could be beneficial in amelioration of these conditions [169]. Further studies are still required to clarify its correlation with an excess of bacteria in the small intestine [94–96].

#### 4.3.4. Neurology

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the elderly population and besides severe motor symptoms it is also associated with GI motility abnormalities [99,170], which may include small intestine dysbiosis as a result of delayed OCTT. Various studies point to a high prevalence of SIBO in PD and the possibility of it aggravating gastrointestinal manifestations [97,101–103,171]. *H. pylori* co-infection also has a synergic impact on the severity of GI symptoms [101,172]. Contrary, Tan et al. proposed a hypothesis that SIBO-positive patients have a benefit and found a reduced constipation score due to increased GI motility, although SIBO in those patients predicted worse motor function [100]. One of the complications of SIBO-malabsorption could also be caused by levodopa, the mainstay of PD treatment [100,173]. The intestinal mucosa is the absorption area for levodopa and its dysfunction due to microflora abnormalities leads to a decreased concentration of dopamine in the target organ–brain. Moreover, excessive bacterial numbers in the gut might induce the production of reactive oxygen species, which aid in the inactivation of the medication and change its bioavailability. That mechanism was also proposed as a cause of weight loss in PD patients, but it was not confirmed in studies [57]. The prevalence of SIBO is not dependent on PD duration—it can be present in the early stage with the same rate [100]. Therefore, the hypothesis that gut dysbiosis is not only the result but also the cause of PD could be meaningful. Small bowel permeability and endotoxemia activate microglia–brain tissue responsible for neuroinflammation [100]. Furthermore, the intestinal microbiota is considered a potential activator of  $\alpha$ -synuclein, a protein inhibitor of dopamine synthesis, and the other “offender” in PD pathogenesis [174]. A hypothesis proposes that improvement of the bacterial status in the gut might have a positive influence on manifestation like also the progress of Parkinson's disease, but further research is crucial.

Nowadays, autism spectrum disorders (ASDs) are increasingly diagnosed. The pathogenesis of the disease is still unknown. Exacerbating factors are looked for due to differences in course. The severity of autism is divided into three groups (mild, moderate, severe) and it is measured with the Autism Treatment Evaluation Checklist (ATEC) [175]. Additionally,

GI manifestations are needed to be assessed with an altered version of the GI Severity Index [176]. A few studies show a significant modification in intestinal bacterial composition. Higher levels of Bacteroidetes or *Clostridium perfringens* were observed in the autistic population [177]. Contrary, healthy controls presented a greater concentration of Firmicutes [178]. The prevalence of SIBO in autism could even reach above 20% [104]. Wang et al. reported that SIBO was related to the severity of ASD. Children with higher ATEC score presented more intense GI symptoms., which were improved after oral pharmacotherapy with non-absorbable antibiotics [104]. Several pathomechanisms are mentioned as likely causes of these relationships. Firstly, propionate overproduction by Clostridia species could lead to neurological impact as well as modified bacterial metabolism of aromatic acids [179]. Secondly, malabsorption, including vitamin B12 malabsorption is observed in the course of SIBO [180]. Persistent cobalamin deficiency may yield neurological and psychiatric disorders by glutathione deficiency as a result of higher antioxidant take-up [181]. Finally, LPS of Gram-negative bacteria leads to higher permeability of the blood-brain barrier by inducing inflammatory status in the brain [182]. It could generate toxins (like mercury), responsible for aggravating the course of autism, in the central nervous system. Unfortunately, most research was performed on animals and additional studies are necessary to confirm those hypotheses on humans. However, a confirmed relationship between SIBO and ASD may create new treatment possibilities in the autistic population that would improve their quality of life.

Brain Fogginess (BF)—a rare neurological condition, also known as D-lactate encephalopathy, is induced by elevated intestinal production and absorption of D-lactate due to D-lactic acidosis. Neurological BF manifestations, like confusion, slurred speech, ataxia, and impaired short-term memory are accompanied by abdominal pain, belching, or flatulence, though initially, it was associated only with short bowel syndrome. The main cause is the abundance of *Lactobacillus* and *Bifidobacterium* species, which are responsible for the fermentation of carbohydrate substrates due to excessive production of D-lactate [105,183]. Furthermore, the mentioned disturbances were observed not only in patients with short bowel syndrome. Rao et al. described the possible relation of BF to gut dysbiosis. In their research, the occurrence of SIBO and D-lactic acidosis was significantly higher in subjects with BF than in those without BF. However, further investigations are essential due to many different limitations of the study [105].

#### 4.3.5. Rheumatology and Cutaneous Diseases

Systemic sclerosis (SSc, scleroderma) is a chronic, connective tissue disorder of autoimmune etiology, which leads to fibrosis of numerous organs [109,184]. GI tract, starting with the esophagus and following with the large and small intestine, may be afflicted by a pathological process in up to 90% of patients [185–187]. Approximately 55% of patients suffer from gastrointestinal symptoms, like bloating, constipation, abdominal pain, or diarrhea [106,109,188], which substantially influences their quality of life [106]. Dysmotility, which manifests as prolonged OCTT and impaired bowel clearance, could be a risk factor for the development of SIBO [106,109]. The co-occurrence of SSc and SIBO was confirmed in various studies [106,108,110–114]. Disease duration of longer than 5 years is a significant risk factor for SIBO development [109]. Mortality in scleroderma is influenced by one of the major complications of gut bacteria excess—malnutrition [185,187], hence it is proposed that SIBO should be diagnosed and cured at an early stage [112]. Lower levels of protein, vitamin B12, and ferritin were observed in SIBO-positive subjects contrary to SIBO-negatives [107]. Jejunal bacteria are responsible for the deconjugation of bile salts and insufficient absorption of fat and fat-soluble vitamins like A or K [189]. Screening is suggested, when the global symptoms score (GSS) of digestive symptoms is greater than 5 [107]. The GSS incorporates abdominal pain, vomiting, bloating, or diarrhea [190]. Antibiotics, especially rifaximin 1200 mg daily, are commonly used during eradication, mainly because of their safety and efficacy. Reduction of gastrointestinal symptoms was observed after completion of therapy in systemic sclerosis patients [106,188]. Additionally,

as evidenced by recent studies, probiotics like *Saccharomyces boulardii* may be effective in the reduction of manifestations from the GI tract, sometimes even in combination with metronidazole [114]. However, more research is still required to routinely treat all patients in that manner [191].

Although rosacea is classified as a dermatosis, manifesting with erythema and phy-matous changes of the facial area [192], patients frequently complain of gastrointestinal disorders as well [193]. Rosacea subjects demonstrate the occurrence of SIBO more frequently than control groups. Furthermore, disturbances of the small gut microbiota were confirmed as a potential trigger of rosacea. The proposed pathogenesis seems to be the presence of bacterial antigens in the bloodstream and the production of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). Interestingly, treatment with rifaximin can achieve a reduction or re-mission of dermatosis in SIBO-positive patients, which confirms a relationship between bowel microbiome and rosacea [115,116]. More studies are still needed to elucidate the mechanisms of the aforementioned processes.

#### 4.3.6. Nephrology

Gut-kidney axis is a novel research area undertaken by dozens of scientists. All current findings point out a huge impact of intestinal milieu on renal functionality. In chronic kidney disease (CKD) the majority of patients suffer from GI manifestation. Kidney failure predisposes to changes in the intestinal microbiome as well as in the gastroenterointestinal system. Overgrowth of aerobic and proteolytic bacteria in the duodenum and jejunum is observed in the CKD population. Expansion of Enterobacteriaceae and Enterococci species with a relative deficit of Lactobacillus, Prevotella, or Bifidobacterium seems to be meaningful [194]. Moreover, modifications in the microscopic structure of the lumen (enlargement of the crypts, decrease of villous, penetration of lamina propria with inflammatory cells, disarrangement of epithelial tight junction) are present in CKD [195]. Solutes, generated by bacteria (such as indoxyl sulfate or p-cresol sulfate), are normally eliminated with urine, consequently, this process is disturbed in CKD [196]. The prevalence of SIBO reaches up to 36% and it is significantly higher than in healthy controls [117]. Uremia is proposed to be the culprit of this complication. Uremic toxins act on the autonomic nervous system and establish conditions for bacterial growth by aggravating intestinal motility. On the other hand, CKD contributes to a rise in intestinal permeability and penetration of antigens into the bloodstream [197]. Toxins may be intercepted by anion transporters in the tubules, which leads to the deterioration of the kidney [198]. This could be one explanation for the influence of intestinal dysbiosis on the progression of CKD.

Acute kidney injury (AKI) is another disease where studies show that lack of exposure to normal microbiota induces less immune deviation and reduces immune regulation [199]. Ischemia-reperfusion injury (IRI), as the leading trigger of AKI [200], could induce intestinal dysbiosis and exacerbate kidney injury by boosting inflammation consequently. Yang et al. discovered that the reduction of gut microbiota in mice may have renoprotective qualities by depletion of Th17, Th1 response and progress of Tregs, and M2-polarized macrophage [201]. Additionally, intestinal microbiota by secretion of SCFAs, which diminish inflammation in the kidney, could control systemic implications of AKI [202].

Immunoglobulin A (IgA) is abundant in the intestinal tract. Chronic pro-inflammatory stage and an excessive number of gut microbiota boost epithelium and lymphocytes B to IgA production. Therefore, intestinal dysbiosis is considered a risk factor for the development of IgA nephropathy [203]. Genome-wide association studies have identified risk loci in genes involved in the maintenance of the intestinal epithelial barrier and response to mucosal pathogens. The genetic risk of IgA nephropathy also strongly correlates with microbiota variation, particularly helminth diversity [204].

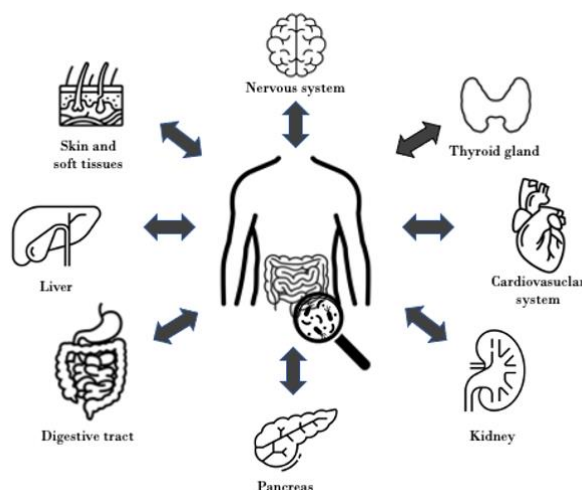
The kidney-gut axis seems to also play a role in hypertension development. Studies have shown that both in animal models and a small sample of patients there is a decrease in the microbial abundance, diversity, and an increased Firmicutes/Bacteroidetes ratio. A microbiome-oriented intervention (minocycline) reduced blood pressure values [205]. An-

other paper revealed a relationship between gut dysbiosis and blood pressure in obstructive sleep apnea-induced hypertension [206].

A small study also suggests that all kidney stone formers have a distinct gut microbiome (both *Bacteroides* and *Prevotella* abundance were associated with nephrolithiasis) [207]. However, data on the direct relationship between kidney diseases and SIBO is still lacking, and detailed research is crucial so that it could be applied in future diagnosis and treatment.

## 5. Conclusions

In conclusion, SIBO is a frequent condition, and many factors could promote its development. Although there are different types of diagnostic tests, none is perfect, that's why new diagnostic strategies are being sought. Bacterial dysbiosis is observed not only in patients with gastrointestinal symptoms but also related to other systemic diseases. Multiple studies confirm a constellation of correlations between digestive, cardiovascular, endocrine, neurological, nephrological, connective tissue, or dermatological disorders and SIBO confirming its multifactorial impact on various medical problems (Figure 2). Some of them are more complex, others just a trifle. They all show the prominent impact that gut microbiota has on our organism. However, additional research is crucial to verify many faces of SIBO. Antibiotic therapy could reduce not only GI symptoms but also manifestations of underlying pathology, hence the quality of life could be improved. This creates new treatment directions for many well-known diseases. However, the biggest problem of most studies cited is little number and diversity of tested groups and the requirement of verification in other similar studies. Moreover, a lot of findings are based on animal models and have not been confirmed in humans. The other problem is the disparity in diagnostic methods as well as the variety of SIBO manifestations. It makes it impossible to compare studies' results with each other. Finally, a lot of conditions described in this paper were connected only with gut microbiota status but not directly with SIBO. While these studies may have some limitations, they still provide valuable insights and have the potential to impact future research in this area. These studies can serve as a foundation for further investigation and can help to identify new directions for research. Despite their limitations, these studies highlight the complexity of SIBO and the need for continued investigation into this important area of study.



**Figure 2.** Bidirectional relationships between altered intestinal microbiota and different regions of the human body.



**Author Contributions:** Conceptualization, N.S. and A.R.-R.; methodology, K.K.; software, T.H.; validation, A.R.-R., K.K. and T.H.; formal analysis, N.S., A.R.-R., M.R. and I.G.; investigation, I.G.; resources, T.H.; data curation, K.K.; writing—original draft preparation, N.S.; writing—review and editing, A.R.-R., K.K., M.R., I.G. and T.H.; visualization, N.S.; supervision, A.R.-R.; project administration, N.S.; funding acquisition, T.H. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable in this article.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

- Robles-Alonso, V.; Guarner, F. Progress in the knowledge of the intestinal human microbiota. *Nutricion Hospitalaria* **2013**, *28*, 553–557. [\[CrossRef\]](#)
- Jethwani, P.; Grover, K. Gut Microbiota in Health and Diseases—A Review. *Int. J. Curr. Microbiol. App. Sci.* **2019**, *8*, 1586–1599. [\[CrossRef\]](#)
- Gomaa, E.Z. Human Gut Microbiota/Microbiome in Health and Diseases: A Review. *Antonie Van Leeuwenhoek* **2020**, *113*, 2019–2040. [\[CrossRef\]](#) [\[PubMed\]](#)
- Corazza, G.R.; Menozzi, M.G.; Stocchi, A.; Rasciti, L.; Vaira, D.; Lecchini, R.; Avanzini, P.; Chezzi, C.; Gasbarrini, G. The Diagnosis of Small Bowel Bacterial Overgrowth. *Gastroenterology* **1990**, *98*, 302–309. [\[CrossRef\]](#)
- Adike, A.; DiBaise, J.K. Small Intestinal Bacterial Overgrowth. *Gastroenterol. Clin. N. Am.* **2018**, *47*, 193–208. [\[CrossRef\]](#)
- Enko, D.; Kriegshäuser, G. Functional <sup>13</sup>C-Urea and Glucose Hydrogen/Methane Breath Tests Reveal Significant Association of Small Intestinal Bacterial Overgrowth in Individuals with Active *Helicobacter Pylori* Infection. *Clin. Biochem.* **2017**, *50*, 46–49. [\[CrossRef\]](#)
- Pimentel, M.; Chow, E.J.; Lin, H.C. Normalization of Lactulose Breath Testing Correlates with Symptom Improvement in Irritable Bowel Syndrome: A Double-Blind, Randomized, Placebo-Controlled Study. *Am. J. Gastroenterol.* **2003**, *98*, 412–419. [\[CrossRef\]](#)
- Pimentel, M. A Link between Irritable Bowel Syndrome and Fibromyalgia May Be Related to Findings on Lactulose Breath Testing. *Ann. Rheum. Dis.* **2004**, *63*, 450–452. [\[CrossRef\]](#)
- Walters, B.; Vanner, S.J. Detection of Bacterial Overgrowth in IBS Using the Lactulose H<sub>2</sub> Breath Test: Comparison with <sup>14</sup>C-d-Xylose and Healthy Controls. *Am. J. Gastroenterol.* **2005**, *100*, 1566–1570. [\[CrossRef\]](#)
- Lupascu, A.; Gabrielli, M.; Lauritano, E.C.; Scarpellini, E.; Santoliquido, A.; Cammarota, G.; Flore, R.; Tondi, P.; Pola, P.; Gasbarrini, G.; et al. Hydrogen Glucose Breath Test to Detect Small Intestinal Bacterial Overgrowth: A Prevalence Case-Control Study in Irritable Bowel Syndrome. *Aliment. Pharm.* **2005**, *22*, 1157–1160. [\[CrossRef\]](#)
- Posserud, I.; Stotzer, P.-O.; Björnsson, E.S.; Abrahamsson, H.; Simrén, M. Small Intestinal Bacterial Overgrowth in Patients with Irritable Bowel Syndrome. *Gut* **2007**, *56*, 802–808. [\[CrossRef\]](#) [\[PubMed\]](#)
- Bratten, J.R.; Spanier, J.; Jones, M.P. Lactulose Breath Testing Does Not Discriminate Patients with Irritable Bowel Syndrome from Healthy Controls. *Am. J. Gastroenterol.* **2008**, *103*, 958–963. [\[CrossRef\]](#) [\[PubMed\]](#)
- Park, J.H.; Park, D.I.; Kim, H.J.; Cho, Y.K.; Sohn, C.I.; Jeon, W.K.; Kim, B.I.; Won, K.H.; Park, S.M. The Relationship between Small-Intestinal Bacterial Overgrowth and Intestinal Permeability in Patients with Irritable Bowel Syndrome. *Gut Liver* **2009**, *3*, 174–179. [\[CrossRef\]](#)
- Parodi, A.; Dulbecco, P.; Savarino, E.; Giannini, E.G.; Bodini, G.; Corbo, M.; Isola, L.; De Conca, S.; Marabotto, E.; Savarino, V. Positive Glucose Breath Testing Is More Prevalent in Patients with IBS-like Symptoms Compared with Controls of Similar Age and Gender Distribution. *J. Clin. Gastroenterol.* **2009**, *43*, 962–966. [\[CrossRef\]](#)
- Ghoshal, U.C.; Kumar, S.; Mehrotra, M.; Lakshmi, C.; Misra, A. Frequency of Small Intestinal Bacterial Overgrowth in Patients with Irritable Bowel Syndrome and Chronic Non-Specific Diarrhea. *J. Neurogastroenterol. Motil.* **2010**, *16*, 40–46. [\[CrossRef\]](#)
- Rana, S.V.; Sharma, S.; Kaur, J.; Sinha, S.K.; Singh, K. Comparison of Lactulose and Glucose Breath Test for Diagnosis of Small Intestinal Bacterial Overgrowth in Patients with Irritable Bowel Syndrome. *Digestion* **2012**, *85*, 243–247. [\[CrossRef\]](#) [\[PubMed\]](#)
- Sachdeva, S.; Rawat, A.K.; Reddy, R.S.; Puri, A.S. Small Intestinal Bacterial Overgrowth (SIBO) in Irritable Bowel Syndrome: Frequency and Predictors: SIBO in IBS: Frequency and Predictors. *J. Gastroenterol. Hepatol.* **2011**, *26*, 135–138. [\[CrossRef\]](#)
- Ghoshal, U.C.; Srivastava, D.; Ghoshal, U.; Misra, A. Breath Tests in the Diagnosis of Small Intestinal Bacterial Overgrowth in Patients with Irritable Bowel Syndrome in Comparison with Quantitative Upper Gut Aspirate Culture. *Eur. J. Gastroenterol. Hepatol.* **2014**, *26*, 753–760. [\[CrossRef\]](#)
- Abbasi, M.H.; Zahedi, M.; Darvish Moghadam, S.; Shafieipour, S.; HayatBakhsh Abbasi, M. Small Bowel Bacterial Overgrowth in Patients with Irritable Bowel Syndrome: The First Study in Iran. *Middle East J. Dig. Dis.* **2015**, *7*, 36–40.

20. Zhao, J.; Zheng, X.; Chu, H.; Zhao, J.; Cong, Y.; Fried, M.; Fox, M.; Dai, N. A Study of the Methodological and Clinical Validity of the Combined Lactulose Hydrogen Breath Test with Scintigraphic Oro-Cecal Transit Test for Diagnosing Small Intestinal Bacterial Overgrowth in IBS Patients. *Neurogastroenterol. Motil.* **2014**, *26*, 794–802. [\[CrossRef\]](#)
21. Rutgeerts, P.; Ghos, Y.; Vantrappen, G.; Eyssen, H. Ileal Dysfunction and Bacterial Overgrowth in Patients with Crohn's Disease. *Eur. J. Clin. Investig.* **1981**, *11*, 199–206. [\[CrossRef\]](#)
22. Castiglione, F.; Del Vecchio Blanco, G.; Rispo, A.; Petrelli, G.; Amalfi, G.; Cozzolino, A.; Cuccaro, I.; Mazzacca, G. Orocecal Transit Time and Bacterial Overgrowth in Patients with Crohn's Disease. *J. Clin. Gastroenterol.* **2000**, *31*, 63–66. [\[CrossRef\]](#)
23. Klaus, J.; Spaniol, U.; Adler, G.; Mason, R.A.; Reinshagen, M.; von Tirpitz, C.C. Small Intestinal Bacterial Overgrowth Mimicking Acute Flare as a Pitfall in Patients with Crohn's Disease. *BMC Gastroenterol.* **2009**, *9*, 61. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Greco, A.; Caviglia, G.P.; Brignolo, P.; Ribaldone, D.G.; Reggiani, S.; Sguazzini, C.; Smedile, A.; Pellicano, R.; Resegotti, A.; Astegiano, M.; et al. Glucose Breath Test and Crohn's Disease: Diagnosis of Small Intestinal Bacterial Overgrowth and Evaluation of Therapeutic Response. *Scand. J. Gastroenterol.* **2015**, *50*, 1376–1381. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Ricci, J.E.R.; Chebli, L.A.; Ribeiro, T.C.d.R.; Castro, A.C.S.; Gaburri, P.D.; Pace, F.H.d.L.; Barbosa, K.V.B.D.; Ferreira, L.E.V.V.d.C.; Passos, M.d.C.F.; Malaguti, C.; et al. Small-Intestinal Bacterial Overgrowth Is Associated with Concurrent Intestinal Inflammation but Not with Systemic Inflammation in Crohn's Disease Patients. *J. Clin. Gastroenterol.* **2018**, *52*, 530–536. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Rana, S.V.; Sharma, S.; Kaur, J.; Prasad, K.K.; Sinha, S.K.; Kochhar, R.; Malik, A.; Morya, R.K. Relationship of Cytokines, Oxidative Stress and GI Motility with Bacterial Overgrowth in Ulcerative Colitis Patients. *J. Crohn's Colitis* **2014**, *8*, 859–865. [\[CrossRef\]](#)
27. Yang, C.; Zhang, X.; Wang, S.; Huo, X.; Wang, J. Small Intestinal Bacterial Overgrowth and Evaluation of Intestinal Barrier Function in Patients with Ulcerative Colitis. *Am. J. Transl. Res.* **2021**, *13*, 6605–6610.
28. Rana, S.V.; Sharma, S.; Malik, A.; Kaur, J.; Prasad, K.K.; Sinha, S.K.; Singh, K. Small Intestinal Bacterial Overgrowth and Orocecal Transit Time in Patients of Inflammatory Bowel Disease. *Dig. Dis. Sci.* **2013**, *58*, 2594–2598. [\[CrossRef\]](#)
29. Lee, J.M.; Lee, K.-M.; Chung, Y.Y.; Lee, Y.W.; Kim, D.B.; Sung, H.J.; Chung, W.C.; Paik, C.-N. Clinical Significance of the Glucose Breath Test in Patients with Inflammatory Bowel Disease. *J. Gastroenterol. Hepatol.* **2015**, *30*, 990–994. [\[CrossRef\]](#)
30. Andrei, M.; Gologan, S. Small Intestinal Bacterial Overgrowth Syndrome Prevalence in Romanian Patients with Inflammatory Bowel Disease. *Curr. Health Sci. J.* **2016**, 151–156. [\[CrossRef\]](#)
31. Ghoshal, U.C.; Yadav, A.; Fatima, B.; Agrahari, A.P.; Misra, A. Small Intestinal Bacterial Overgrowth in Patients with Inflammatory Bowel Disease: A Case-Control Study. *Indian, J. Gastroenterol.* **2022**, *41*, 96–103. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Prizont, R.; Hersh, T.; Floch, M.H. Jejunal Bacterial Flora in Chronic Small Bowel Disease. *Am. J. Clin. Nutr.* **1970**, *23*, 1602–1607. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Tursi, A.; Brandimarte, G.; Giorgetti, G. High Prevalence of Small Intestinal Bacterial Overgrowth in Celiac Patients with Persistence of Gastrointestinal Symptoms after Gluten Withdrawal. *Am. J. Gastroenterol.* **2003**, *98*, 839–843. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Ghoshal, U.C.; Ghoshal, U.; Misra, A.; Choudhuri, G. Partially Responsive Celiac Disease Resulting from Small Intestinal Bacterial Overgrowth and Lactose Intolerance. *BMC Gastroenterol.* **2004**, *4*, 10. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Rana, S.V.; Sinha, S.K.; Lal, S.; Sikander, A.; Singh, K. Small Intestinal Bacterial Overgrowth in North Indian Patients with Celiac Disease. *Trop. Gastroenterol.* **2007**, *28*, 159–161.
36. Rubio-Tapia, A.; Barton, S.H.; Rosenblatt, J.E.; Murray, J.A. Prevalence of Small Intestine Bacterial Overgrowth Diagnosed by Quantitative Culture of Intestinal Aspirate in Celiac Disease. *J. Clin. Gastroenterol.* **2009**, *43*, 157–161. [\[CrossRef\]](#)
37. Chang, M.S.; Minaya, M.T.; Cheng, J.; Connor, B.A.; Lewis, S.K.; Green, P.H.R. Double-Blind Randomized Controlled Trial of Rifaximin for Persistent Symptoms in Patients with Celiac Disease. *Dig. Dis. Sci.* **2011**, *56*, 2939–2946. [\[CrossRef\]](#)
38. Lasa, J.S.; Zubiaurre, I.; Fanjul, I.; Olivera, P.; Soifer, L. Small Intestinal Bacterial Overgrowth Prevalence in Celiac Disease Patients Is Similar in Healthy Subjects and Lower in Irritable Bowel Syndrome Patients. *Rev. Gastroenterol. México (Engl. Ed.)* **2015**, *80*, 171–174. [\[CrossRef\]](#)
39. Paik, C.N.; Choi, M.-G.; Lim, C.H.; Park, J.M.; Chung, W.C.; Lee, K.-M.; Jun, K.-H.; Song, K.Y.; Jeon, H.M.; Chin, H.-M.; et al. The Role of Small Intestinal Bacterial Overgrowth in Postgastrectomy Patients: Bacterial Overgrowth and Gastrectomy. *Neurogastroenterol. Motil.* **2011**, *23*, e191–e196. [\[CrossRef\]](#)
40. Heneghan, H.M.; Zaborowski, A.; Fanning, M.; McHugh, A.; Doyle, S.; Moore, J.; Ravi, N.; Reynolds, J.V. Prospective Study of Malabsorption and Malnutrition After Esophageal and Gastric Cancer Surgery. *Ann. Surg.* **2015**, *262*, 803–808. [\[CrossRef\]](#)
41. Sabate, J.-M.; Coupaye, M.; Ledoux, S.; Castel, B.; Msika, S.; Coffin, B.; Jouet, P. Consequences of Small Intestinal Bacterial Overgrowth in Obese Patients Before and After Bariatric Surgery. *Obes. Surg.* **2017**, *27*, 599–605. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Kim, D.B.; Paik, C.-N.; Kim, Y.J.; Lee, J.M.; Jun, K.-H.; Chung, W.C.; Lee, K.-M.; Yang, J.-M.; Choi, M.-G. Positive Glucose Breath Tests in Patients with Hysterectomy, Gastrectomy, and Cholecystectomy. *Gut Liver* **2017**, *11*, 237–242. [\[CrossRef\]](#)
43. Rao, S.S.C.; Tan, G.; Abdulla, H.; Yu, S.; Larion, S.; Leelasinjaroen, P. Does Colectomy Predispose to Small Intestinal Bacterial (SIBO) and Fungal Overgrowth (SIFO)? *Clin. Transl. Gastroenterol.* **2018**, *9*, e146. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Mouillot, T.; Rhyman, N.; Gauthier, C.; Paris, J.; Lang, A.-S.; Lepers-Tassy, S.; Manfredi, S.; Lepage, C.; Leloup, C.; Jacquin-Piques, A.; et al. Study of Small Intestinal Bacterial Overgrowth in a Cohort of Patients with Abdominal Symptoms Who Underwent Bariatric Surgery. *Obes. Surg.* **2020**, *30*, 2331–2337. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Sabaté, J.-M.; Jouët, P.; Harnois, F.; Mechler, C.; Msika, S.; Grossin, M.; Coffin, B. High Prevalence of Small Intestinal Bacterial Overgrowth in Patients with Morbid Obesity: A Contributor to Severe Hepatic Steatosis. *Obes. Surg.* **2008**, *18*, 371–377. [\[CrossRef\]](#) [\[PubMed\]](#)

46. Madrid, A.M.; Poniachik, J.; Quera, R.; Defilippi, C. Small Intestinal Clustered Contractions and Bacterial Overgrowth: A Frequent Finding in Obese Patients. *Dig. Dis. Sci.* **2011**, *56*, 155–160. [\[CrossRef\]](#)
47. Fialho, A.; Fialho, A.; Thota, P.; McCullough, A.; Shen, B. Higher Visceral to Subcutaneous Fat Ratio Is Associated with Small Intestinal Bacterial Overgrowth. *Nutr. Metab. Cardiovasc. Dis.* **2016**, *26*, 773–777. [\[CrossRef\]](#)
48. Roland, B.C.; Lee, D.; Miller, L.S.; Vegesna, A.; Yolken, R.; Severance, E.; Prandovszky, E.; Zheng, X.E.; Mullin, G.E. Obesity Increases the Risk of Small Intestinal Bacterial Overgrowth (SIBO). *Neurogastroenterol. Motil.* **2018**, *30*, e13199. [\[CrossRef\]](#)
49. Wigg, A.J.; Roberts-Thomson, I.C.; Dymock, R.B.; McCarthy, P.J.; Grose, R.H.; Cummins, A.G. The Role of Small Intestinal Bacterial Overgrowth, Intestinal Permeability, Endotoxaemia, and Tumour Necrosis Factor Alpha in the Pathogenesis of Non-Alcoholic Steatohepatitis. *Gut* **2001**, *48*, 206–211. [\[CrossRef\]](#)
50. Sajjad, A.; Mottershead, M.; Syn, W.K.; Jones, R.; Smith, S.; Nwokolo, C.U. Ciprofloxacin Suppresses Bacterial Overgrowth, Increases Fasting Insulin but Does Not Correct Low Acylated Ghrelin Concentration in Non-Alcoholic Steatohepatitis. *Aliment. Pharm.* **2005**, *22*, 291–299. [\[CrossRef\]](#)
51. Miele, L.; Valenza, V.; La Torre, G.; Montalto, M.; Cammarota, G.; Ricci, R.; Mascianà, R.; Forgione, A.; Gabrieli, M.L.; Perotti, G.; et al. Increased Intestinal Permeability and Tight Junction Alterations in Nonalcoholic Fatty Liver Disease. *Hepatology* **2009**, *49*, 1877–1887. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Shanab, A.A.; Scully, P.; Crosbie, O.; Buckley, M.; O'Mahony, L.; Shanahan, F.; Gazareen, S.; Murphy, E.; Quigley, E.M.M. Small Intestinal Bacterial Overgrowth in Nonalcoholic Steatohepatitis: Association with Toll-Like Receptor 4 Expression and Plasma Levels of Interleukin 8. *Dig. Dis. Sci.* **2011**, *56*, 1524–1534. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Fialho, A.; Fialho, A.; Thota, P.; McCullough, A.J.; Shen, B. Small Intestinal Bacterial Overgrowth Is Associated with Non-Alcoholic Fatty Liver Disease. *JGLD* **2016**, *25*, 159–165. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Ghoshal, U.C.; Baba, C.S.; Ghoshal, U.; Alexander, G.; Misra, A.; Saraswat, V.A.; Choudhuri, G. Low-Grade Small Intestinal Bacterial Overgrowth Is Common in Patients with Non-Alcoholic Steatohepatitis on Quantitative Jejunal Aspirate Culture. *Indian J. Gastroenterol.* **2017**, *36*, 390–399. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Mikolasevic, I.; Delija, B.; Mijic, A.; Stevanovic, T.; Skenderevic, N.; Sosa, I.; Krznaric-Zrnic, I.; Abram, M.; Krznaric, Z.; Domislovic, V.; et al. Small Intestinal Bacterial Overgrowth and Non-Alcoholic Fatty Liver Disease Diagnosed by Transient Elastography and Liver Biopsy. *Int. J. Clin. Pract.* **2021**, *75*, e13947. [\[CrossRef\]](#)
56. Shi, H.; Mao, L.; Wang, L.; Quan, X.; Xu, X.; Cheng, Y.; Zhu, S.; Dai, F. Small Intestinal Bacterial Overgrowth and Orocecal Transit Time in Patients of Nonalcoholic Fatty Liver Disease. *Eur. J. Gastroenterol. Hepatol.* **2021**, *33*, e535–e539. [\[CrossRef\]](#)
57. Chesta, J.; Silva, M.; Thompson, L.; del Canto, E.; Defilippi, C. Bacterial overgrowth in small intestine in patients with liver cirrhosis. *Rev. Med. Chil.* **1991**, *119*, 626–632.
58. Casafont Morencos, F.; de las Heras Castano, G.; Martín Ramos, L.; López Arias, M.J.; Ledesma, F.; Pons Romero, F. Small Bowel Bacterial Overgrowth in Patients with Alcoholic Cirrhosis. *Dig. Dis. Sci.* **1995**, *40*, 1252–1256. [\[CrossRef\]](#)
59. Madrid, A.M.; Cumsille, F.; Defilippi, C. Altered Small Bowel Motility in Patients with Liver Cirrhosis Depends on Severity of Liver Disease. *Dig. Dis. Sci.* **1997**, *42*, 738–742. [\[CrossRef\]](#)
60. Yang, C.-Y.; Chang, C.-S.; Chen, G.-H. Small- Intestinal Bacterial Overgrowth in Patients with Liver Cirrhosis, Diagnosed with Glu- Cose H2 or CH4 Breath Tests. *Scand. J. Gastroenterol.* **1998**, *33*, 867–871. [\[CrossRef\]](#)
61. Bauer, T.M.; Schwacha, H.; Steinbrückner, B.; Brinkmann, F.E.; Ditzen, A.K.; Kist, M.; Blum, H.E. Diagnosis of Small Intestinal Bacterial Overgrowth in Patients with Cirrhosis of the Liver: Poor Performance of the Glucose Breath Hydrogen Test. *J. Hepatol.* **2000**, *33*, 382–386. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Gunnarsdottir, S.A.; Sadik, R.; Shev, S.; Simren, M.; Sjøvall, H.; Stotzer, P.-O.; Abrahamsson, H.; Olsson, R.; Björnsson, E.S. Small Intestinal Motility Disturbances and Bacterial Overgrowth in Patients with Liver Cirrhosis and Portal Hypertension. *Am. J. Gastroenterol.* **2003**, *98*, 1362–1370. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Nancey, S.; Moussata, D.; Roman, S.; Benmansour, H.; Claudel, S.; Flourié, B. A Positive Breath Hydrogen Test Does Not Predict the Occurrence of a Spontaneous Bacterial Peritonitis in Cirrhotic Patients with Ascites. *Digestion* **2009**, *79*, 252–258. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Pande, C.; Kumar, A.; Sarin, S.K. Small-Intestinal Bacterial Overgrowth in Cirrhosis Is Related to the Severity of Liver Disease. *Aliment. Pharmacol. Ther.* **2009**, *29*, 1273–1281. [\[CrossRef\]](#)
65. Jun, D.W.; Kim, K.T.; Lee, O.Y.; Chae, J.D.; Son, B.K.; Kim, S.H.; Jo, Y.J.; Park, Y.S. Association Between Small Intestinal Bacterial Overgrowth and Peripheral Bacterial DNA in Cirrhotic Patients. *Dig. Dis. Sci.* **2010**, *55*, 1465–1471. [\[CrossRef\]](#)
66. Gupta, A.; Dhiman, R.K.; Kumari, S.; Rana, S.; Agarwal, R.; Duseja, A.; Chawla, Y. Role of Small Intestinal Bacterial Overgrowth and Delayed Gastrointestinal Transit Time in Cirrhotic Patients with Minimal Hepatic Encephalopathy. *J. Hepatol.* **2010**, *53*, 849–855. [\[CrossRef\]](#)
67. Zhang, Y.; Feng, Y.; Cao, B.; Tian, Q. The Effect of Small Intestinal Bacterial Overgrowth on Minimal Hepatic Encephalopathy in Patients with Cirrhosis. *Arch. Med. Sci.* **2016**, *12*, 592–596. [\[CrossRef\]](#)
68. Kaur, J.; Rana, S.V.; Gupta, R.; Gupta, V.; Sharma, S.K.; Dhawan, D.K. Prolonged Orocecal Transit Time Enhances Serum Bile Acids Through Bacterial Overgrowth, Contributing Factor to Gallstone Disease. *J. Clin. Gastroenterol.* **2014**, *48*, 365–369. [\[CrossRef\]](#)
69. Kim, D.B.; Paik, C.-N.; Song, D.S.; Kim, Y.J.; Lee, J.M. The Characteristics of Small Intestinal Bacterial Overgrowth in Patients with Gallstone Diseases: Gallstone Diseases and SIBO. *J. Gastroenterol. Hepatol.* **2018**, *33*, 1477–1484. [\[CrossRef\]](#)



70. Casellas, F.; Guarner, L.; Vaquero, E.; Antolín, M.; de Gracia, X.; Malagelada, J.R. Hydrogen Breath Test with Glucose in Exocrine Pancreatic Insufficiency. *Pancreas* **1998**, *16*, 481–486. [\[CrossRef\]](#)
71. Trespi, E.; Ferrieri, A. Intestinal Bacterial Overgrowth During Chronic Pancreatitis. *Curr. Med. Res. Opin.* **1999**, *15*, 47–52. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Signoretti, M.; Stigliano, S.; Valente, R.; Piciocchi, M.; Fave, G.D.; Capurso, G. Small Intestinal Bacterial Overgrowth in Patients With Chronic Pancreatitis. *J. Clin. Gastroenterol.* **2014**, *48*, S52–S55. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Kumar, K.; Ghoshal, U.C.; Srivastava, D.; Misra, A.; Mohindra, S. Small Intestinal Bacterial Overgrowth Is Common Both among Patients with Alcoholic and Idiopathic Chronic Pancreatitis. *Pancreatol.* **2014**, *14*, 280–283. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Kim, D.B.; Paik, C.-N.; Sung, H.J.; Chung, W.C.; Lee, K.-M.; Yang, J.-M.; Choi, M.-G. Breath Hydrogen and Methane Are Associated with Intestinal Symptoms in Patients with Chronic Pancreatitis. *Pancreatol.* **2015**, *15*, 514–518. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Ní Chonchubhair, H.M.; Bashir, Y.; Dobson, M.; Ryan, B.M.; Duggan, S.N.; Conlon, K.C. The Prevalence of Small Intestinal Bacterial Overgrowth in Non-Surgical Patients with Chronic Pancreatitis and Pancreatic Exocrine Insufficiency (PEI). *Pancreatol.* **2018**, *18*, 379–385. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Lee, A.A.; Baker, J.R.; Wamsteker, E.J.; Saad, R.; DiMagno, M.J. Small Intestinal Bacterial Overgrowth Is Common in Chronic Pancreatitis and Associates with Diabetes, Chronic Pancreatitis Severity, Low Zinc Levels, and Opiate Use. *Am. J. Gastroenterol.* **2019**, *114*, 1163–1171. [\[CrossRef\]](#)
77. Zhang, M.; Zhu, H.-M.; He, F.; Li, B.-Y.; Li, X.-C. Association between Acute Pancreatitis and Small Intestinal Bacterial Overgrowth Assessed by Hydrogen Breath Test. *WJG* **2017**, *23*, 8591–8596. [\[CrossRef\]](#)
78. Kim, D.B.; Paik, C.-N.; Lee, J.M.; Kim, Y.-J. Association between Increased Breath Hydrogen Methane Concentration and Prevalence of Glucose Intolerance in Acute Pancreatitis. *J. Breath Res.* **2020**, *14*, 026006. [\[CrossRef\]](#)
79. Lisowska, A.; Wójtowicz, J.; Walkowiak, J. Small Intestine Bacterial Overgrowth Is Frequent in Cystic Fibrosis: Combined Hydrogen and Methane Measurements Are Required for Its Detection. *Acta Biochim. Pol.* **2009**, *56*, 631–634. [\[CrossRef\]](#)
80. Dorsey, J.; Gonska, T. Bacterial Overgrowth, Dysbiosis, Inflammation, and Dysmotility in the Cystic Fibrosis Intestine. *J. Cyst. Fibros.* **2017**, *16*, S14–S23. [\[CrossRef\]](#)
81. Furnari, M.; De Alessandri, A.; Cresta, F.; Haupt, M.; Bassi, M.; Calvi, A.; Haupt, R.; Bodini, G.; Ahmed, I.; Bagnasco, F.; et al. The Role of Small Intestinal Bacterial Overgrowth in Cystic Fibrosis: A Randomized Case-Controlled Clinical Trial with Rifaximin. *J. Gastroenterol.* **2019**, *54*, 261–270. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Pasini, E.; Aquilani, R.; Testa, C.; Baiardi, P.; Angioletti, S.; Boschi, F.; Verri, M.; Dioguardi, F. Pathogenic Gut Flora in Patients with Chronic Heart Failure. *JACC Heart Fail.* **2016**, *4*, 220–227. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Song, Y.; Liu, Y.; Qi, B.; Cui, X.; Dong, X.; Wang, Y.; Han, X.; Li, F.; Shen, D.; Zhang, X.; et al. Association of Small Intestinal Bacterial Overgrowth with Heart Failure and Its Prediction for Short-Term Outcomes. *JAHA* **2021**. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Ponziani, F.R.; Pompili, M.; Di Stasio, E.; Zocco, M.A.; Gasbarrini, A.; Flore, R. Subclinical Atherosclerosis Is Linked to Small Intestinal Bacterial Overgrowth via Vitamin K2-Dependent Mechanisms. *WJG* **2017**, *23*, 1241. [\[CrossRef\]](#)
85. Fialho, A.; Fialho, A.; Kochhar, G.; Schenone, A.L.; Thota, P.; McCullough, A.J.; Shen, B. Association Between Small Intestinal Bacterial Overgrowth by Glucose Breath Test and Coronary Artery Disease. *Dig. Dis. Sci.* **2018**, *63*, 412–421. [\[CrossRef\]](#)
86. Fialho, A.; Fialho, A.; Schenone, A.; Thota, P.; McCullough, A.; Shen, B. Association between Small Intestinal Bacterial Overgrowth and Deep Vein Thrombosis. *Gastroenterol. Rep.* **2016**, *4*, 299–303. [\[CrossRef\]](#)
87. Cheng, X.; Zhang, L.; Xie, N.-C.; Xu, H.-L.; Lian, Y.-J. Association between Small-intestinal Bacterial Overgrowth and Deep Vein Thrombosis in Patients with Spinal Cord Injuries. *J. Thromb. Haemost.* **2017**, *15*, 304–311. [\[CrossRef\]](#)
88. Ojetti, V.; Pitocco, D.; Scarpellini, E.; Zaccardi, F.; Scaldaferrri, F.; Gigante, G.; Gasbarrini, G.; Ghirlanda, G.; Gasbarrini, A. Small Bowel Bacterial Overgrowth and Type 1 Diabetes. *Eur. Rev. Med. Pharm. Sci.* **2009**, *13*, 419–423.
89. Faria, M.; Pavin, E.J.; Parisi, M.C.R.; Lorena, S.L.S.; Brunetto, S.Q.; Ramos, C.D.; Pavan, C.R.; Mesquita, M.A. Delayed Small Intestinal Transit in Patients with Long-Standing Type 1 Diabetes Mellitus: Investigation of the Relationships with Clinical Features, Gastric Emptying, Psychological Distress, and Nutritional Parameters. *Diabetes. Technol. Ther.* **2013**, *15*, 32–38. [\[CrossRef\]](#)
90. Malik, A.; Morya, R.K.; Bhadada, S.K.; Rana, S. Type 1 Diabetes Mellitus: Complex Interplay of Oxidative Stress, Cytokines, Gastrointestinal Motility and Small Intestinal Bacterial Overgrowth. *Eur. J. Clin. Investig.* **2018**, *48*, e13021. [\[CrossRef\]](#)
91. Rana, S.; Bhansali, A.; Bhadada, S.; Sharma, S.; Kaur, J.; Singh, K. Orocecal Transit Time and Small Intestinal Bacterial Overgrowth in Type 2 Diabetes Patients from North India. *Diabetes Technol. Ther.* **2011**, *13*, 1115–1120. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Rana, S.V.; Malik, A.; Bhadada, S.K.; Sachdeva, N.; Morya, R.K.; Sharma, G. Malabsorption, Orocecal Transit Time and Small Intestinal Bacterial Overgrowth in Type 2 Diabetic Patients: A Connection. *Ind. J. Clin. Biochem.* **2017**, *32*, 84–89. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Zietz, B.; Lock, G.; Straub, R.H.; Braun, B.; Scholmerich, J.; Palitzsch, K.D. Small-Bowel Bacterial Overgrowth in Diabetic Subjects Is Associated with Cardiovascular Autonomic Neuropathy. *Diabetes Care* **2000**, *23*, 1200–1201. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Lauritano, E.C.; Bilotta, A.L.; Gabrielli, M.; Scarpellini, E.; Lupascu, A.; Laginestra, A.; Novi, M.; Sottili, S.; Serricchio, M.; Cammarota, G.; et al. Association between Hypothyroidism and Small Intestinal Bacterial Overgrowth. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 4180–4184. [\[CrossRef\]](#)
95. Brechmann, T.; Sperlbauer, A.; Schmiegel, W. Levthyroxine Therapy and Impaired Clearance Are the Strongest Contributors to Small Intestinal Bacterial Overgrowth: Results of a Retrospective Cohort Study. *WJG* **2017**, *23*, 842. [\[CrossRef\]](#)

96. Konrad, P.; Chojnacki, J.; Kaczka, A.; Pawłowicz, M.; Rudnicki, C.; Chojnacki, C. Thyroid dysfunction in patients with small intestinal bacterial overgrowth. *Pol. Merkur. Lek.* **2018**, *44*, 15–18.
97. Gabrielli, M.; Bonazzi, P.; Scarpellini, E.; Bendia, E.; Lauritano, E.C.; Fasano, A.; Ceravolo, M.G.; Capecci, M.; Rita Bentivoglio, A.; Provinciali, L.; et al. Prevalence of Small Intestinal Bacterial Overgrowth in Parkinson's Disease. *Mov. Disord.* **2011**, *26*, 889–892. [\[CrossRef\]](#)
98. Dobbs, R.; Charlett, A.; Dobbs, S.M.; Weller, C.; Ibrahim, M.A.A.; Iguodala, O.; Smee, C.; Plant, J.; Lawson, A.J.; Taylor, D.; et al. Leukocyte-Subset Counts in Idiopathic Parkinsonism Provide Clues to a Pathogenic Pathway Involving Small Intestinal Bacterial Overgrowth. A Surveillance Study. *Gut Pathog.* **2012**, *4*, 12. [\[CrossRef\]](#)
99. Fasano, A.; Visanji, N.P.; Liu, L.W.C.; Lang, A.E.; Pfeiffer, R.F. Gastrointestinal Dysfunction in Parkinson's Disease. *Lancet Neurol.* **2015**, *14*, 625–639. [\[CrossRef\]](#)
100. Tan, A.H.; Mahadeva, S.; Thalha, A.M.; Gibson, P.R.; Kiew, C.K.; Yeat, C.M.; Ng, S.W.; Ang, S.P.; Chow, S.K.; Tan, C.T.; et al. Small Intestinal Bacterial Overgrowth in Parkinson's Disease. *Park. Relat. Disord.* **2014**, *20*, 535–540. [\[CrossRef\]](#)
101. Niu, X.-L.; Liu, L.; Song, Z.-X.; Li, Q.; Wang, Z.-H.; Zhang, J.-L.; Li, H.-H. Prevalence of Small Intestinal Bacterial Overgrowth in Chinese Patients with Parkinson's Disease. *J. Neural. Transm.* **2016**, *123*, 1381–1386. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Su, A.; Gandhi, R.; Barlow, C.; Triadafilopoulos, G. Utility of the Wireless Motility Capsule and Lactulose Breath Testing in the Evaluation of Patients with Parkinson's Disease Who Present with Functional Gastrointestinal Symptoms. *BMJ Open Gastroenterol.* **2017**, *4*, e000132. [\[CrossRef\]](#) [\[PubMed\]](#)
103. Hasuike, Y.; Endo, T.; Koroyasu, M.; Matsui, M.; Mori, C.; Yamadera, M.; Fujimura, H.; Sakoda, S. Bile Acid Abnormality Induced by Intestinal Dysbiosis Might Explain Lipid Metabolism in Parkinson's Disease. *Med. Hypotheses* **2020**, *134*, 109436. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Wang, L.; Yu, Y.-M.; Zhang, Y.; Zhang, J.; Lu, N.; Liu, N. Hydrogen Breath Test to Detect Small Intestinal Bacterial Overgrowth: A Prevalence Case–Control Study in Autism. *Eur. Child Adolesc. Psychiatry* **2018**, *27*, 233–240. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Rao, S.S.C.; Rehman, A.; Yu, S.; Andino, N.M. de Brain Fogginess, Gas and Bloating: A Link between SIBO, Probiotics and Metabolic Acidosis. *Clin. Transl. Gastroenterol.* **2018**, *9*, 162. [\[CrossRef\]](#)
106. Parodi, A.; Sessarego, M.; Greco, A.; Bazzica, M.; Filaci, G.; Setti, M.; Savarino, E.; Indiveri, F.; Savarino, V.; Ghio, M. Small Intestinal Bacterial Overgrowth in Patients Suffering from Scleroderma: Clinical Effectiveness of Its Eradication. *Am. J. Gastroenterol.* **2008**, *103*, 1257–1262. [\[CrossRef\]](#)
107. Marie, I.; Ducrotte, P.; Denis, P.; Menard, J.-F.; Levesque, H. Small Intestinal Bacterial Overgrowth in Systemic Sclerosis. *Rheumatology* **2009**, *48*, 1314–1319. [\[CrossRef\]](#)
108. Fynne, L.; Worsøe, J.; Gregersen, T.; Schlageter, V.; Laurberg, S.; Krogh, K. Gastrointestinal Transit in Patients with Systemic Sclerosis. *Scand. J. Gastroenterol.* **2011**, *46*, 1187–1193. [\[CrossRef\]](#)
109. Savarino, E.; Mei, F.; Parodi, A.; Ghio, M.; Furnari, M.; Gentile, A.; Berdini, M.; Di Sario, A.; Bendia, E.; Bonazzi, P.; et al. Gastrointestinal Motility Disorder Assessment in Systemic Sclerosis. *Rheumatology* **2013**, *52*, 1095–1100. [\[CrossRef\]](#)
110. Gemignani, L.; Savarino, V.; Ghio, M.; Parodi, A.; Zentilin, P.; de Bortoli, N.; Negrini, S.; Furnari, M.; Dulbecco, P.; Giamb Bruno, E.; et al. Lactulose Breath Test to Assess Oro-Cecal Transit Delay and Estimate Esophageal Dysmotility in Scleroderma Patients. *Semin. Arthritis Rheum.* **2013**, *42*, 522–529. [\[CrossRef\]](#)
111. Marie, I.; Leroi, A.-M.; Menard, J.-F.; Levesque, H.; Quillard, M.; Ducrotte, P. Fecal Calprotectin in Systemic Sclerosis and Review of the Literature. *Autoimmun. Rev.* **2015**, *14*, 547–554. [\[CrossRef\]](#) [\[PubMed\]](#)
112. Adarsh, M.B.; Sharma, S.K.; Sinha, S.K.; Bhattacharya, A.; Rana, S.; Dhir, V.; Singh, S. Gastrointestinal Dysmotility and Infections in Systemic Sclerosis- An Indian Scenario. *Curr. Rheumatol. Rev.* **2018**, *14*, 172–176. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Sawadpanich, K.; Soison, P.; Chunlertrith, K.; Mairiang, P.; Sukeepaisarnjaroen, W.; Sangchan, A.; Suttichaimongkol, T.; Foocharoen, C. Prevalence and Associated Factors of Small Intestinal Bacterial Overgrowth among Systemic Sclerosis Patients. *Int. J. Rheum. Dis.* **2019**, *22*, 695–699. [\[CrossRef\]](#) [\[PubMed\]](#)
114. García-Collinot, G.; Madrigal-Santillán, E.O.; Martínez-Bencomo, M.A.; Carranza-Muleiro, R.A.; Jara, L.J.; Vera-Lastra, O.; Montes-Cortes, D.H.; Medina, G.; Cruz-Domínguez, M.P. Effectiveness of *Saccharomyces Boulardii* and Metronidazole for Small Intestinal Bacterial Overgrowth in Systemic Sclerosis. *Dig. Dis. Sci.* **2019**, *65*, 1134–1143. [\[CrossRef\]](#)
115. Parodi, A.; Paolino, S.; Greco, A.; Drago, F.; Mansi, C.; Rebora, A.; Parodi, A.; Savarino, V. Small Intestinal Bacterial Overgrowth in Rosacea: Clinical Effectiveness of Its Eradication. *Clin. Gastroenterol. Hepatol.* **2008**, *6*, 759–764. [\[CrossRef\]](#)
116. Drago, F.; De Col, E.; Agnoletti, A.F.; Schiavetti, I.; Savarino, V.; Rebora, A.; Paolino, S.; Cozzani, E.; Parodi, A. The Role of Small Intestinal Bacterial Overgrowth in Rosacea: A 3-Year Follow-Up. *J. Am. Acad. Dermatol.* **2016**, *75*, e113–e115. [\[CrossRef\]](#)
117. Strid, H.; Simrén, M.; Stotzer, P.-O.; Ringström, G.; Abrahamsson, H.; Björnsson, E.S. Patients with Chronic Renal Failure Have Abnormal Small Intestinal Motility and a High Prevalence of Small Intestinal Bacterial Overgrowth. *Digestion* **2003**, *67*, 129–137. [\[CrossRef\]](#)
118. Bernhardt, H.; Knoke, M. Recent Studies on the Microbial Ecology of the Upper Gastrointestinal Tract. *Infection* **1989**, *17*, 259–263. [\[CrossRef\]](#)
119. Dukowicz, A.C.; Lacy, B.E.; Levine, G.M. Small Intestinal Bacterial Overgrowth: A Comprehensive Review. *Gastroenterol. Hepatol.* **2007**, *3*, 112–122.



120. Bouhnik, Y.; Alain, S.; Attar, A.; Flourié, B.; Raskine, L.; Sanson-Le Pors, M.J.; Rambaud, J.-C. Bacterial Populations Contaminating The Upper Gut in Patients With Small Intestinal Bacterial Overgrowth Syndrome. *Am. J. Gastroenterol.* **1999**, *94*, 1327–1331. [\[CrossRef\]](#)
121. Rezaie, A.; Buresi, M.; Lembo, A.; Lin, H.; McCallum, R.; Rao, S.; Schmulson, M.; Valdovinos, M.; Zakko, S.; Pimentel, M. Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus. *Am. J. Gastroenterol.* **2017**, *112*, 775–784. [\[CrossRef\]](#) [\[PubMed\]](#)
122. Roland, B.C.; Ciarleglio, M.M.; Clarke, J.O.; Semler, J.R.; Tomakin, E.; Mullin, G.E.; Pasricha, P.J. Low Ileocecal Valve Pressure Is Significantly Associated with Small Intestinal Bacterial Overgrowth (SIBO). *Dig. Dis. Sci.* **2014**, *59*, 1269–1277. [\[CrossRef\]](#) [\[PubMed\]](#)
123. Khoshini, R.; Dai, S.-C.; Lezcano, S.; Pimentel, M. A Systematic Review of Diagnostic Tests for Small Intestinal Bacterial Overgrowth. *Dig. Dis. Sci.* **2008**, *53*, 1443–1454. [\[CrossRef\]](#) [\[PubMed\]](#)
124. Jacobs, C.; Coss Adame, E.; Attaluri, A.; Valestin, J.; Rao, S.S.C. Dysmotility and Proton Pump Inhibitor Use Are Independent Risk Factors for Small Intestinal Bacterial and/or Fungal Overgrowth. *Aliment. Pharm.* **2013**, *37*, 1103–1111. [\[CrossRef\]](#) [\[PubMed\]](#)
125. Lombardo, L.; Foti, M.; Ruggia, O.; Chiecchio, A. Increased Incidence of Small Intestinal Bacterial Overgrowth During Proton Pump Inhibitor Therapy. *Clin. Gastroenterol. Hepatol.* **2010**, *8*, 504–508. [\[CrossRef\]](#)
126. Saltzman, J.R.; Kowdley, K.V.; Pedrosa, M.C.; Sepe, T.; Golner, B.; Perrone, G.; Russell, R.M. Bacterial Overgrowth without Clinical Malabsorption in Elderly Hypochlorhydric Subjects. *Gastroenterology* **1994**, *106*, 615–623. [\[CrossRef\]](#)
127. Gray, J.D.; Shiner, M. Influence of Gastric PH on Gastric and Jejunal Flora. *Gut* **1967**, *8*, 574–581. [\[CrossRef\]](#)
128. Weston, A.P.; Biddle, W.L.; Bhatia, P.S.; Miner, P.B. Terminal Ileal Mucosal Mast Cells in Irritable Bowel Syndrome. *Dig. Dis. Sci.* **1993**, *38*, 1590–1595. [\[CrossRef\]](#)
129. Salzmänn, J.L.; Peltier-Koch, F.; Bloch, F.; Petite, J.P.; Camilleri, J.P. Morphometric Study of Colonic Biopsies: A New Method of Estimating Inflammatory Diseases. *Lab. Investig.* **1989**, *60*, 847–851.
130. Lin, H.C. Small Intestinal Bacterial Overgrowth: A Framework for Understanding Irritable Bowel Syndrome. *JAMA* **2004**, *292*, 852–858. [\[CrossRef\]](#)
131. Aziz, I.; Törnblom, H.; Simrén, M. Small Intestinal Bacterial Overgrowth as a Cause for Irritable Bowel Syndrome: Guilty or Not Guilty? *Curr. Opin. Gastroenterol.* **2017**, *33*, 196–202. [\[CrossRef\]](#) [\[PubMed\]](#)
132. Pimentel, M.; Mathur, R.; Chang, C. Gas and the Microbiome. *Curr. Gastroenterol. Rep.* **2013**, *15*, 356. [\[CrossRef\]](#) [\[PubMed\]](#)
133. Cohen-Mekelburg, S.; Tafesh, Z.; Coburn, E.; Weg, R.; Malik, N.; Webb, C.; Hammad, H.; Scherl, E.; Bosworth, B.P. Testing and Treating Small Intestinal Bacterial Overgrowth Reduces Symptoms in Patients with Inflammatory Bowel Disease. *Dig. Dis. Sci.* **2018**, *63*, 2439–2444. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Fraquelli, M.; Bardella, M.T.; Peracchi, M.; Cesana, B.M.; Bianchi, P.A.; Conte, D. Gallbladder Emptying and Somatostatin and Cholecystokinin Plasma Levels in Celiac Disease. *Am. J. Gastroenterol.* **1999**, *94*, 1866–1870. [\[CrossRef\]](#)
135. Bardella, M.T.; Fraquelli, M.; Peracchi, M.; Cesana, B.M.; Bianchi, P.A. Gastric Emptying and Plasma Neurotensin Levels in Untreated Celiac Patients. *Scand. J. Gastroenterol.* **2000**, *35*, 269–273. [\[CrossRef\]](#)
136. Remes-Troche, J.M.; Adames, K.; Castillo-Rodal, A.I.; Ramírez, T.; Barreto-Zuñiga, R.; López-Vidal, Y.; Uscanga, L.F. Intraepithelial  $\Gamma\delta$  Lymphocytes: A Comparative Study between Celiac Disease, Small Intestinal Bacterial Overgrowth, and Irritable Bowel Syndrome. *J. Clin. Gastroenterol.* **2007**, *41*, 671–676. [\[CrossRef\]](#) [\[PubMed\]](#)
137. Chalasani, N.; Younossi, Z.; Lavine, J.E.; Diehl, A.M.; Brunt, E.M.; Cusi, K.; Charlton, M.; Sanyal, A.J. The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* **2012**, *55*, 2005–2023. [\[CrossRef\]](#)
138. Araújo, A.R.; Rosso, N.; Bedogni, G.; Tiribelli, C.; Bellentani, S. Global Epidemiology of Non-Alcoholic Fatty Liver Disease/Non-Alcoholic Steatohepatitis: What We Need in the Future. *Liver Int.* **2018**, *38* (Suppl. 1), 47–51. [\[CrossRef\]](#)
139. Mouzaki, M.; Comelli, E.M.; Arendt, B.M.; Bonengel, J.; Fung, S.K.; Fischer, S.E.; McGilvray, I.D.; Allard, J.P. Intestinal Microbiota in Patients with Nonalcoholic Fatty Liver Disease. *Hepatology* **2013**, *58*, 120–127. [\[CrossRef\]](#)
140. Wang, Z.; Klipfell, E.; Bennett, B.J.; Koeth, R.; Levison, B.S.; DuGar, B.; Feldstein, A.E.; Britt, E.B.; Fu, X.; Chung, Y.-M.; et al. Gut Flora Metabolism of Phosphatidylcholine Promotes Cardiovascular Disease. *Nature* **2011**, *472*, 57–63. [\[CrossRef\]](#)
141. Zhu, L.; Baker, S.S.; Gill, C.; Liu, W.; Alkhouri, R.; Baker, R.D.; Gill, S.R. Characterization of Gut Microbiomes in Nonalcoholic Steatohepatitis (NASH) Patients: A Connection between Endogenous Alcohol and NASH. *Hepatology* **2013**, *57*, 601–609. [\[CrossRef\]](#) [\[PubMed\]](#)
142. Yadav, D.; Timmons, L.; Benson, J.T.; Dierkhising, R.A.; Chari, S.T. Incidence, Prevalence, and Survival of Chronic Pancreatitis: A Population-Based Study. *Am. J. Gastroenterol.* **2011**, *106*, 2192–2199. [\[CrossRef\]](#) [\[PubMed\]](#)
143. Ghoshal, U.C. How to Interpret Hydrogen Breath Tests. *J. Neurogastroenterol. Motil.* **2011**, *17*, 312–317. [\[CrossRef\]](#) [\[PubMed\]](#)
144. Tan, C.; Ling, Z.; Huang, Y.; Cao, Y.; Liu, Q.; Cai, T.; Yuan, H.; Liu, C.; Li, Y.; Xu, K. Dysbiosis of Intestinal Microbiota Associated with Inflammation Involved in the Progression of Acute Pancreatitis. *Pancreas* **2015**, *44*, 868–875. [\[CrossRef\]](#)
145. De Lisle, R.C. Altered Transit and Bacterial Overgrowth in the Cystic Fibrosis Mouse Small Intestine. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **2007**, *293*, G104–G111. [\[CrossRef\]](#) [\[PubMed\]](#)
146. Li, L.; Somerset, S. Digestive System Dysfunction in Cystic Fibrosis: Challenges for Nutrition Therapy. *Dig. Liver Dis.* **2014**, *46*, 865–874. [\[CrossRef\]](#) [\[PubMed\]](#)

147. Sandek, A.; Bjarnason, I.; Volk, H.-D.; Crane, R.; Meddings, J.B.; Niebauer, J.; Kalra, P.R.; Buhner, S.; Herrmann, R.; Springer, J.; et al. Studies on Bacterial Endotoxin and Intestinal Absorption Function in Patients with Chronic Heart Failure. *Int. J. Cardiol.* **2012**, *157*, 80–85. [\[CrossRef\]](#)
148. Katsimichas, T.; Ohtani, T.; Motooka, D.; Tsukamoto, Y.; Kioka, H.; Nakamoto, K.; Konishi, S.; Chimura, M.; Sengoku, K.; Miyawaki, H.; et al. Non-Ischemic Heart Failure with Reduced Ejection Fraction Is Associated with Altered Intestinal Microbiota. *Circ. J.* **2018**, *82*, 1640–1650. [\[CrossRef\]](#)
149. Sandek, A.; Swidsinski, A.; Schroedl, W.; Watson, A.; Valentova, M.; Herrmann, R.; Scherbakov, N.; Cramer, L.; Rauchhaus, M.; Grosse-Herrenthey, A.; et al. Intestinal Blood Flow in Patients with Chronic Heart Failure. *J. Am. Coll. Cardiol.* **2014**, *64*, 1092–1102. [\[CrossRef\]](#)
150. Mollar, A.; Villanueva, M.P.; NÚÑez, E.; Carratalá, A.; Mora, F.; Bayés-Genís, A.; Mínguez, M.; Marrachelli, V.G.; Monleon, D.; Navarro, D.; et al. Hydrogen- and Methane-Based Breath Testing and Outcomes in Patients with Heart Failure. *J. Card. Fail.* **2019**, *25*, 319–327. [\[CrossRef\]](#)
151. Niebauer, J.; Volk, H.-D.; Kemp, M.; Dominguez, M.; Schumann, R.R.; Rauchhaus, M.; Poole-Wilson, P.A.; Coats, A.J.; Anker, S.D. Endotoxin and Immune Activation in Chronic Heart Failure: A Prospective Cohort Study. *Lancet* **1999**, *353*, 1838–1842. [\[CrossRef\]](#)
152. Sandek, A.; Rauchhaus, M.; Anker, S.D.; von Haehling, S. The Emerging Role of the Gut in Chronic Heart Failure. *Curr. Opin. Clin. Nutr. Metab. Care* **2008**, *11*, 632–639. [\[CrossRef\]](#) [\[PubMed\]](#)
153. Anker, S.D.; von Haehling, S. Inflammatory Mediators in Chronic Heart Failure: An Overview. *Heart* **2004**, *90*, 464–470. [\[CrossRef\]](#) [\[PubMed\]](#)
154. Mayerhofer, C.C.K.; Awoyemi, A.O.; Moscovitch, S.D.; Lappegård, K.T.; Hov, J.R.; Aukrust, P.; Hovland, A.; Lorenzo, A.; Halvorsen, S.; Seljeflot, I.; et al. Design of the GutHeart-Targeting Gut Microbiota to Treat Heart Failure-Trial: A Phase II, Randomized Clinical Trial: GutHeart Design. *ESC Heart Fail.* **2018**, *5*, 977–984. [\[CrossRef\]](#) [\[PubMed\]](#)
155. Tang, W.H.W.; Wang, Z.; Levison, B.S.; Koeth, R.A.; Britt, E.B.; Fu, X.; Wu, Y.; Hazen, S.L. Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk. *N. Engl. J. Med.* **2013**, *368*, 1575–1584. [\[CrossRef\]](#)
156. Chen, M.; Yi, L.; Zhang, Y.; Zhou, X.; Ran, L.; Yang, J.; Zhu, J.; Zhang, Q.; Mi, M. Resveratrol Attenuates Trimethylamine- N -Oxide (TMAO)-Induced Atherosclerosis by Regulating TMAO Synthesis and Bile Acid Metabolism via Remodeling of the Gut Microbiota. *mBio* **2016**, *7*, e02210-15. [\[CrossRef\]](#)
157. Virally-Monod, M.; Tiélmans, D.; Kevorkian, J.P.; Bouhnik, Y.; Flourie, B.; Porokhov, B.; Ajzenberg, C.; Warnet, A.; Guillausseau, P.J. Chronic Diarrhoea and Diabetes Mellitus: Prevalence of Small Intestinal Bacterial Overgrowth. *Diabetes Metab.* **1998**, *24*, 530–536.
158. Shi, H.; Kokoeva, M.V.; Inouye, K.; Tzamelis, I.; Yin, H.; Flier, J.S. TLR4 Links Innate Immunity and Fatty Acid-Induced Insulin Resistance. *J. Clin. Investig.* **2006**, *116*, 3015–3025. [\[CrossRef\]](#)
159. Delzenne, N.M.; Cani, P.D.; Everard, A.; Neyrinck, A.M.; Bindels, L.B. Gut Microorganisms as Promising Targets for the Management of Type 2 Diabetes. *Diabetologia* **2015**, *58*, 2206–2217. [\[CrossRef\]](#)
160. Bytzer, P.; Talley, N.J.; Leemon, M.; Young, L.J.; Jones, M.P.; Horowitz, M. Prevalence of Gastrointestinal Symptoms Associated With Diabetes Mellitus: A Population-Based Survey of 15,000 Adults. *Arch. Intern. Med.* **2001**, *161*, 1989. [\[CrossRef\]](#)
161. Reddymasu, S.C.; McCallum, R.W. Small Intestinal Bacterial Overgrowth in Gastroparesis: Are There Any Predictors? *J. Clin. Gastroenterol.* **2010**, *44*, e8–e13. [\[CrossRef\]](#) [\[PubMed\]](#)
162. Vallianou, N.G.; Stratigou, T.; Tsagarakis, S. Microbiome and Diabetes: Where Are We Now? *Diabetes Res. Clin. Pract.* **2018**, *146*, 111–118. [\[CrossRef\]](#) [\[PubMed\]](#)
163. Zaborska, K.E.; Cummings, B.P. Rethinking Bile Acid Metabolism and Signaling for Type 2 Diabetes Treatment. *Curr. Diab. Rep.* **2018**, *18*, 109. [\[CrossRef\]](#) [\[PubMed\]](#)
164. Ciobanu, L.; Dumitrascu, D.L. Gastrointestinal Motility Disorders in Endocrine Diseases. *Pol. Arch. Intern. Med.* **2011**, *121*, 129–136. [\[CrossRef\]](#)
165. Almandoz, J.P.; Gharib, H. Hypothyroidism: Etiology, Diagnosis, and Management. *Med. Clin. N. Am.* **2012**, *96*, 203–221. [\[CrossRef\]](#)
166. Daher, R.; Yazbeck, T.; Jaoude, J.B.; Abboud, B. Consequences of Dysthyroidism on the Digestive Tract and Viscera. *WJG* **2009**, *15*, 2834. [\[CrossRef\]](#)
167. Zhou, L.; Li, X.; Ahmed, A.; Wu, D.; Liu, L.; Qiu, J.; Yan, Y.; Jin, M.; Xin, Y. Gut Microbe Analysis Between Hyperthyroid and Healthy Individuals. *Curr. Microbiol.* **2014**, *69*, 675–680. [\[CrossRef\]](#)
168. Penhale, W.J.; Young, P.R. The Influence of the Normal Microbial Flora on the Susceptibility of Rats to Experimental Autoimmune Thyroiditis. *Clin. Exp. Immunol.* **1988**, *72*, 288–292.
169. Ihnatowicz, P.; Drywień, M.; Wątor, P.; Wojsiat, J. The Importance of Nutritional Factors and Dietary Management of Hashimoto's Thyroiditis. *Ann. Agric. Environ. Med.* **2020**, *27*, 184–193. [\[CrossRef\]](#) [\[PubMed\]](#)
170. Barboza, J.L.; Okun, M.S.; Moshiree, B. The Treatment of Gastroparesis, Constipation and Small Intestinal Bacterial Overgrowth Syndrome in Patients with Parkinson's Disease. *Expert Opin. Pharmacother.* **2015**, *16*, 2449–2464. [\[CrossRef\]](#)
171. DiBaise, J.K.; Crowell, M.D.; Driver-Dunckley, E.; Mehta, S.H.; Hoffman-Snyder, C.; Lin, T.; Adler, C.H. Weight Loss in Parkinson's Disease: No Evidence for Role of Small Intestinal Bacterial Overgrowth. *J. Park. Dis.* **2018**, *571*–581. [\[CrossRef\]](#)

172. Fasano, A.; Bove, F.; Gabrielli, M.; Petracca, M.; Zocco, M.A.; Ragazzoni, E.; Barbaro, F.; Piano, C.; Fortuna, S.; Tortora, A.; et al. The Role of Small Intestinal Bacterial Overgrowth in Parkinson's Disease: Sibo in Parkinson's Disease. *Mov. Disord.* **2013**, *28*, 1241–1249. [[CrossRef](#)] [[PubMed](#)]
173. van Kessel, S.P.; El Aidy, S. Contributions of Gut Bacteria and Diet to Drug Pharmacokinetics in the Treatment of Parkinson's Disease. *Front. Neurol.* **2019**, *10*, 1087. [[CrossRef](#)] [[PubMed](#)]
174. Valles-Colomer, M.; Falony, G.; Darzi, Y.; Tigchelaar, E.F.; Wang, J.; Tito, R.Y.; Schiweck, C.; Kurilshikov, A.; Joossens, M.; Wijnemga, C.; et al. The Neuroactive Potential of the Human Gut Microbiota in Quality of Life and Depression. *Nat. Microbiol.* **2019**, *4*, 623–632. [[CrossRef](#)]
175. Geier, D.A.; Kern, J.K.; Geier, M.R. A Comparison of the Autism Treatment Evaluation Checklist (ATEC) and the Childhood Autism Rating Scale (CARS) for the Quantitative Evaluation of Autism. *J. Ment. Health Res. Intellect. Disabil.* **2013**, *6*, 255–267. [[CrossRef](#)]
176. Cryan, J.F.; Dinan, T.G. Mind-Altering Microorganisms: The Impact of the Gut Microbiota on Brain and Behaviour. *Nat. Rev. Neurosci.* **2012**, *13*, 701–712. [[CrossRef](#)]
177. Finegold, S.M.; Summanen, P.H.; Downes, J.; Corbett, K.; Komoriya, T. Detection of Clostridium Perfringens Toxin Genes in the Gut Microbiota of Autistic Children. *Anaerobe* **2017**, *45*, 133–137. [[CrossRef](#)]
178. Finegold, S.M.; Dowd, S.E.; Gontcharova, V.; Liu, C.; Henley, K.E.; Wolcott, R.D.; Youn, E.; Summanen, P.H.; Granpeesheh, D.; Dixon, D.; et al. Pyrosequencing Study of Fecal Microflora of Autistic and Control Children. *Anaerobe* **2010**, *16*, 444–453. [[CrossRef](#)]
179. Macfabe, D.; Cain, D.; Rodriguezcapote, K.; Franklin, A.; Hoffman, J.; Boon, F.; Taylor, A.; Kavaliers, M.; Ossenkopp, K. Neurobiological Effects of Intraventricular Propionic Acid in Rats: Possible Role of Short Chain Fatty Acids on the Pathogenesis and Characteristics of Autism Spectrum Disorders. *Behav. Brain Res.* **2007**, *176*, 149–169. [[CrossRef](#)]
180. Zhang, Y.; Hodgson, N.W.; Trivedi, M.S.; Abdolmaleky, H.M.; Fournier, M.; Cuenod, M.; Do, K.Q.; Deth, R.C. Decreased Brain Levels of Vitamin B12 in Aging, Autism and Schizophrenia. *PLoS ONE* **2016**, *11*, e0146797. [[CrossRef](#)]
181. Khalighi, A.R.; Khalighi, M.R.; Behdani, R.; Jamali, J.; Khosravi, A.; Kouhestani, S.; Radmanesh, H.; Esmaealzadeh, S.; Khalighi, N. Evaluating the Efficacy of Probiotic on Treatment in Patients with Small Intestinal Bacterial Overgrowth (SIBO)—A Pilot Study. *Indian J. Med. Res.* **2014**, *140*, 604–608. [[PubMed](#)]
182. Adams, J.B.; Romdalvik, J.; Levine, K.E.; Hu, L.-W. Mercury in First-Cut Baby Hair of Children with Autism versus Typically-Developing Children. *Toxicol. Environ. Chem.* **2008**, *90*, 739–753. [[CrossRef](#)]
183. Petersen, C. D-Lactic Acidosis. *Nutr. Clin. Pract.* **2005**, *20*, 634–645. [[CrossRef](#)]
184. Steen, V.D.; Medsger, T.A. Severe Organ Involvement in Systemic Sclerosis with Diffuse Scleroderma. *Arthritis Rheum.* **2000**, *43*, 2437–2444. [[CrossRef](#)] [[PubMed](#)]
185. Gyger, G.; Baron, M. Gastrointestinal Manifestations of Scleroderma: Recent Progress in Evaluation, Pathogenesis, and Management. *Curr. Rheumatol. Rep.* **2012**, *14*, 22–29. [[CrossRef](#)] [[PubMed](#)]
186. Sjogren, R.W. Gastrointestinal Motility Disorders in Scleroderma. *Arthritis Rheum.* **1994**, *37*, 1265–1282. [[CrossRef](#)] [[PubMed](#)]
187. Bharadwaj, S.; Tandon, P.; Gohel, T.; Corrigan, M.L.; Coughlin, K.L.; Shatnawei, A.; Chatterjee, S.; Kirby, D.F. Gastrointestinal Manifestations, Malnutrition, and Role of Enteral and Parenteral Nutrition in Patients with Scleroderma. *J. Clin. Gastroenterol.* **2015**, *49*, 559–564. [[CrossRef](#)]
188. Tian, X.-P. Gastrointestinal Complications of Systemic Sclerosis. *WJG* **2013**, *19*, 7062. [[CrossRef](#)]
189. Stellaard, F.; Sauerbruch, T.; Luderschmidt, C.H.; Leisner, B.; Paumgartner, G. Intestinal Involvement in Progressive Systemic Sclerosis Detected by Increased Unconjugated Serum Bile Acids. *Gut* **1987**, *28*, 446–450. [[CrossRef](#)]
190. Maconi, G. Diagnosis of Symptomatic Uncomplicated Diverticular Disease and the Role of Rifaximin in Management. *Acta Biomed.* **2017**, *88*, 25–32. [[CrossRef](#)]
191. Pittman, N.; Rawn, S.M.; Wang, M.; Masetto, A.; Beattie, K.A.; Larché, M. Treatment of Small Intestinal Bacterial Overgrowth in Systemic Sclerosis: A Systematic Review. *Rheumatology* **2018**, *57*, 1802–1811. [[CrossRef](#)] [[PubMed](#)]
192. Rebora, A. The Management of Rosacea. *Am. J. Clin. Dermatol.* **2002**, *3*, 489–496. [[CrossRef](#)] [[PubMed](#)]
193. Marks, R.; Clark, M.L.; Beard, R.J.; Kwok, M.; Robertson, W.B. Gastrointestinal Observations in Rosacea. *Lancet* **1967**, *289*, 739–743. [[CrossRef](#)]
194. Rukavina Mikusic, N.L.; Kouyoumdzian, N.M.; Choi, M.R. Gut Microbiota and Chronic Kidney Disease: Evidences and Mechanisms That Mediate a New Communication in the Gastrointestinal-Renal Axis. *Pflugers Arch-Eur. J. Physiol.* **2020**, *472*, 303–320. [[CrossRef](#)]
195. Vaziri, N.D.; Dure-Smith, B.; Miller, R.; Mirahmadi, M.K. Pathology of Gastrointestinal Tract in Chronic Hemodialysis Patients: An Autopsy Study of 78 Cases. *Am. J. Gastroenterol.* **1985**, *80*, 608–611.
196. Barrios, C.; Beaumont, M.; Pallister, T.; Villar, J.; Goodrich, J.K.; Clark, A.; Pascual, J.; Ley, R.E.; Spector, T.D.; Bell, J.T.; et al. Gut-Microbiota-Metabolite Axis in Early Renal Function Decline. *PLoS ONE* **2015**, *10*, e0134311. [[CrossRef](#)] [[PubMed](#)]
197. Nallu, A.; Sharma, S.; Ramezani, A.; Muralidharan, J.; Raj, D. Gut Microbiome in Chronic Kidney Disease: Challenges and Opportunities. *Transl. Res.* **2017**, *179*, 24–37. [[CrossRef](#)]
198. Satoh, M.; Hayashi, H.; Watanabe, M.; Ueda, K.; Yamato, H.; Yoshioka, T.; Motojima, M. Uremic Toxins Overload Accelerates Renal Damage in a Rat Model of Chronic Renal Failure. *Nephron. Exp. Nephrol.* **2003**, *95*, e111–e118. [[CrossRef](#)]

199. Jang, H.R.; Gandolfo, M.T.; Ko, G.J.; Satpute, S.; Racusen, L.; Rabb, H. Early Exposure to Germs Modifies Kidney Damage and Inflammation after Experimental Ischemia-Reperfusion Injury. *Am. J. Physiol.-Ren. Physiol.* **2009**, *297*, F1457–F1465. [[CrossRef](#)]
200. Thadhani, R.; Pascual, M.; Bonventre, J.V. Acute Renal Failure. *N. Engl. J. Med.* **1996**, *334*, 1448–1460. [[CrossRef](#)]
201. Yang, J.; Kim, C.J.; Go, Y.S.; Lee, H.Y.; Kim, M.-G.; Oh, S.W.; Cho, W.Y.; Im, S.-H.; Jo, S.K. Intestinal Microbiota Control Acute Kidney Injury Severity by Immune Modulation. *Kidney Int.* **2020**, *98*, 932–946. [[CrossRef](#)] [[PubMed](#)]
202. Andrade-Oliveira, V.; Amano, M.T.; Correa-Costa, M.; Castoldi, A.; Felizardo, R.J.F.; de Almeida, D.C.; Bassi, E.J.; Moraes-Vieira, P.M.; Hiyane, M.I.; Rodas, A.C.D.; et al. Gut Bacteria Products Prevent AKI Induced by Ischemia-Reperfusion. *JASN* **2015**, *26*, 1877–1888. [[CrossRef](#)] [[PubMed](#)]
203. Mahmoodpoor, F.; Rahbar Saadat, Y.; Barzegari, A.; Ardalan, M.; Zununi Vahed, S. The Impact of Gut Microbiota on Kidney Function and Pathogenesis. *Biomed. Pharmacother.* **2017**, *93*, 412–419. [[CrossRef](#)]
204. Kiryluk, K.; Li, Y.; Scolari, F.; Sanna-Cherchi, S.; Choi, M.; Verbitsky, M.; Fasel, D.; Lata, S.; Prakash, S.; Shapiro, S.; et al. Discovery of New Risk Loci for IgA Nephropathy Implicates Genes Involved in Immunity against Intestinal Pathogens. *Nat. Genet.* **2014**, *46*, 1187–1196. [[CrossRef](#)] [[PubMed](#)]
205. Yang, T.; Santisteban, M.M.; Rodriguez, V.; Li, E.; Ahmari, N.; Carvajal, J.M.; Zadeh, M.; Gong, M.; Qi, Y.; Zubcevic, J.; et al. Gut Dysbiosis Is Linked to Hypertension. *Hypertension* **2015**, *65*, 1331–1340. [[CrossRef](#)] [[PubMed](#)]
206. Durgan, D.J.; Ganesh, B.P.; Cope, J.L.; Ajami, N.J.; Phillips, S.C.; Petrosino, J.F.; Hollister, E.B.; Bryan, R.M. Role of the Gut Microbiome in Obstructive Sleep Apnea-Induced Hypertension. *Hypertension* **2016**, *67*, 469–474. [[CrossRef](#)] [[PubMed](#)]
207. Stern, J.M.; Moazami, S.; Qiu, Y.; Kurland, I.; Chen, Z.; Agalliu, I.; Burk, R.; Davies, K.P. Evidence for a Distinct Gut Microbiome in Kidney Stone Formers Compared to Non-Stone Formers. *Urolithiasis* **2016**, *44*, 399–407. [[CrossRef](#)]

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.